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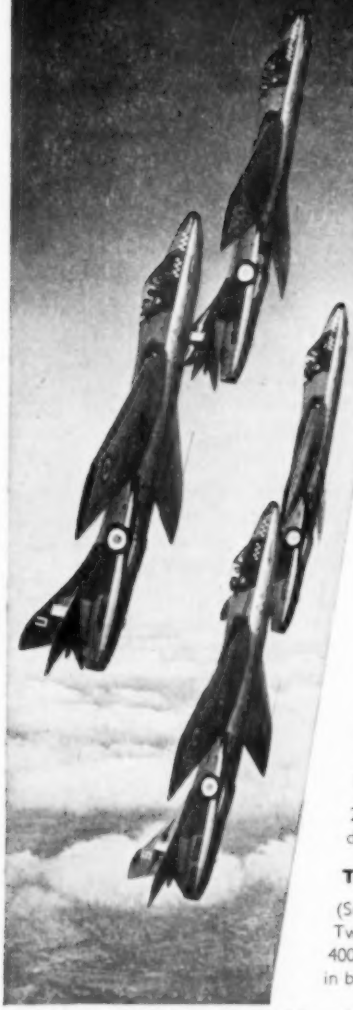

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If applied before the end of the 4th month, it may be easily adjusted by the patient for postpartum wear (to provide proper support for the relaxed abdomen and for muscles and ligaments of the pelvic joints).

For further information write to:

SPENCER (BANBURY) LTD.

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We do not think that anyone would dispute the statement that the art of good lighting consists in seeing, not how many fittings and lamps or how much electricity can be employed, but how well one can see one's surroundings in absolute comfort.

This does not necessarily entail festooning one's rooms with a lot of unnecessary lamps and shades; in fact, if a few well-spaced fittings, such as the one shown in the accompanying illustration, can provide glare-less, shadowless and evenly diffused light everywhere, surely that is the ideal to aim at.

In the daytime there is only one sun to illuminate the whole world, so why, when using artificial light, have innumerable " suns " shining from all directions?—apart from the cost!

Among the most important places in which good lighting should be studied and installed are the surgeries and consulting rooms of doctors, in the interests of their work and their patients, also their own homes, in the interests of themselves and their families.

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The high intensities mentioned are unnecessary and undesirable, for if we normally use no more than we really need, we shall always be able to see by the higher intensities when these occur, whereas if we get used to needlessly high intensities we shall lose the power to see by the lower intensities. Normally about 5 foot-candles should be ample for all ordinary purposes, and when it is considered that a foot-candle simply means the light given by a candle a foot away, it will be realised that 5 foot-candles evenly distributed means that at every point in the room you have the equivalent of 5 candles a foot away. It may be doubted whether there would be enough candles in London to light an average room with this all-round intensity! Yet many so-called experts advocate 10, 20 and even 50 or more foot-candles, which can only cause severe eyestrain, besides being grossly extravagant. Incidentally, the term " foot-candle " was evidently considered too simple and self-explanatory to please the pundits, as it has been changed to " lumens per square foot ", which conveys nothing to the layman. As Oscar Wilde said in one of his plays, " To be intelligible is to be found out "!

The G.V.D. SYSTEM is applicable to every type and size of room and building, and is eminently suitable for hospitals, nursing homes, clinics, waiting rooms, surgeries, consulting rooms, laboratories, lecture halls, libraries, offices, board rooms and of course the home, in fact, wherever good yet economical lighting is required.

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Procidets contain no antibiotic. They are non-toxic and cannot build up resistant strains.

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Cetyl Pyridinium Chloride	*4 mg.*
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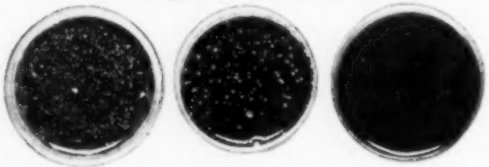
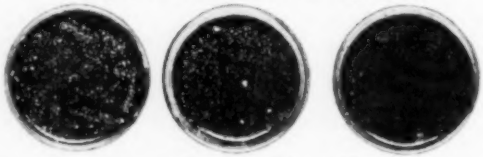
Procidets v Penicillin

Comparative effect on ORAL BACTERIA



Before *After 1 Procidets* *After 4 Procidets*

These photographs are of representative plates showing the dramatic action of Procidets in comparison with Penicillin Lozenge B.P.



Before *After 1 Penicillin Lozenge B.P.* *After 4 Penicillin Lozenges B.P.*

Cartons, all lozenges, metal foil sealed pack.
Retail price 2/5 (incl. P./tax).
Basic N.H.S. cost 1/4 per carton.
Also available dispensing pack 498 lozenges for N.H.S. patients. PROCIDETS prescribable on Form EC10.
Classification category 3/4.

Procidets

Literature and samples on request

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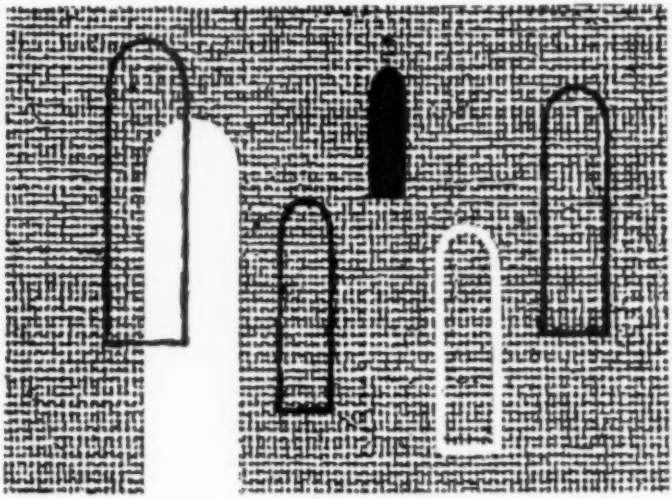

the shape of relief . . .

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The cylindrical shape of ANUSOL suppositories facilitates pain-free insertion and easy retention.
An ANUSOL suppository melts rapidly, bringing soothing and healing medicaments to a wide area of inflamed rectal mucosa.
Active principles: Bismuth subgallate 2.12%, bismuth oxiodogallate 0.03%, bismuth oxide 0.87%, resorcin 0.87%, balsam of Peru 1.77%, zinc oxide 10.60%, boric acid 17.85%, base of cacao butter and beeswax q.s. ad. 100.00%.
Packing: Ointment: 1 oz. tubes. Suppositories in boxes of 12; also boxes of 100 for dispensing purposes at 16/8d (not subject to P.T. on prescription).

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ERYTHROMYCIN

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'Ilotycin' Tablets : 100 mg. and 250 mg. Average dose : 1 Gm. daily.

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Palatable and therapeutically reliable,

the 'Eskacillin' range provides the simplest answer whenever liquid oral penicillin is indicated—*whatever the dosage*. Selection is easy—in each case the number which follows the name 'Eskacillin' equals thousands of international units per standard medical teaspoonful[1]. One word—'Eskacillin'—embraces the whole field of liquid oral penicillin therapy.

ESKACILLIN | 100 | 200 | 300

[1] 1 fl. dr.—3·5 ml.

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A NEW SKF PRODUCT

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PEPTIC ULCER
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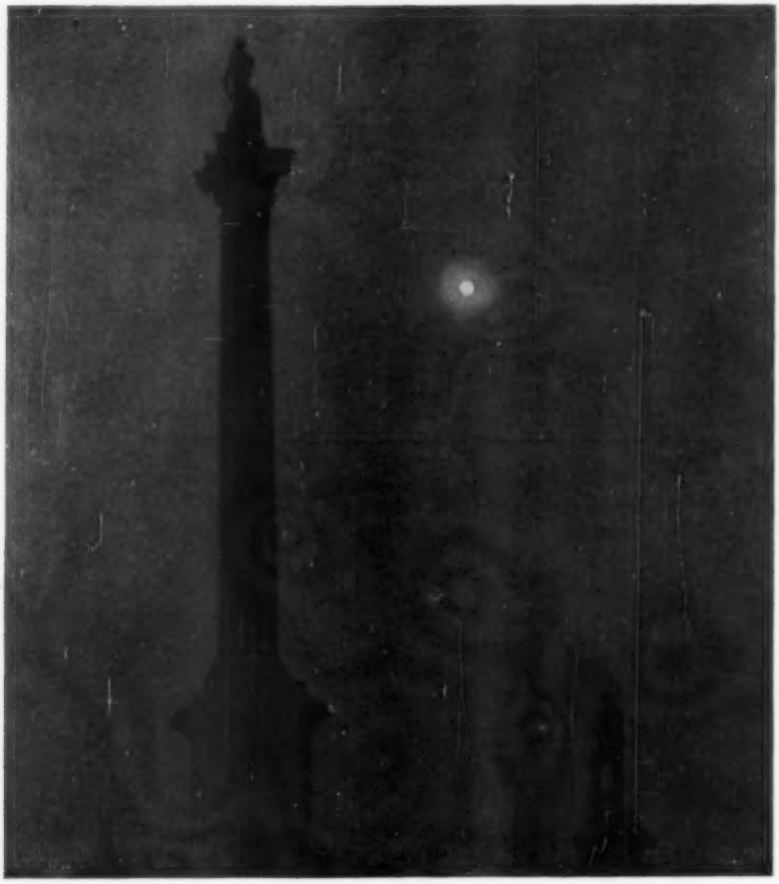

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for the treatment of pneumonia, bronchitis and other respiratory tract infections associated with the dark days.

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PYRIDIUM

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**Practitioner* (1954) 172, 643-4

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CETRIMIDE SHAMPOO

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SEBODERM contains 15.6% of cetrimide, the quaternary ammonium compound specifically recommended for treatment of seborrhoeic dermatitis.

Brit. Med. J., 2 (1951) 1070

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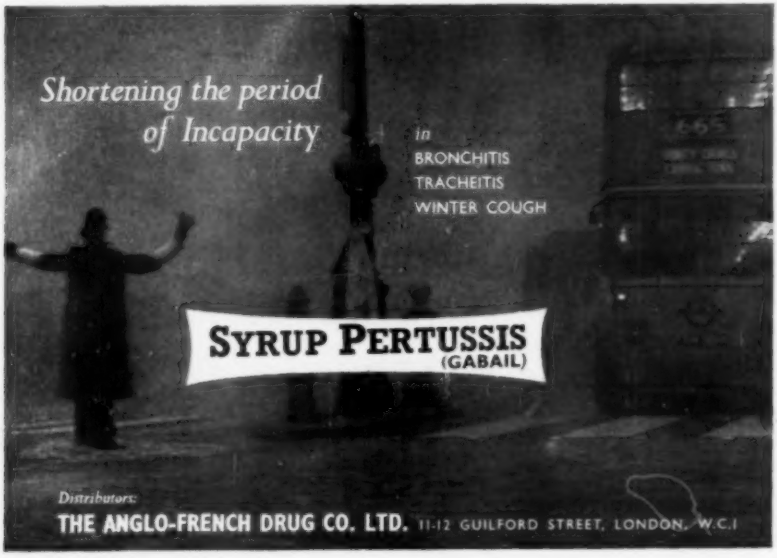

MEGIMIDE BRAND OF BEMEGRIDE

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DAPTAZOLE BRAND OF AMIPHENAZOLE

2: 4-diamino-5-phenylthiazole hydrochloride

Barbiturate and Morphine Antagonists

Further details and supplies of "Megimide" and "Daptazole" available to the medical profession on request.

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MEGIMIDE and DAPTAZOLE

in Barbiturate Poisoning

" MEGIMIDE " is " a barbiturate antagonist of real clinical worth. To omit to use it in the treatment of barbiturate poisoning is to run the risk of the broncho-pneumonia that is so often fatal in these cases." (*Lancet*, 1955, ***i***, 181.)

" DAPTAZOLE," itself a weak barbiturate antagonist, enhances the action of " Megimide."

" Megimide " and " Daptazole " administered together intravenously ensure safe, quick recovery from barbiturate intoxication without the risk of convulsions and secondary depression which often follow the use of other central analeptics.

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IN prolonged, insidious blood loss ; long-standing infections and in protracted dietary deficiencies, as in the elderly, the regeneration of hæmoglobin is usually slow, with the possibility of relapse on cessation of treatment.

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ANTALBY BAILLY

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FOR ADULT AND CHILD MEDICATION

Active constituent: Theophylline para-aminobenzoate of Piperazine

ANTALBY possesses a rapid and effective action in relief of spasm of the bronchial musculature and stimulates the respiratory centre.

INDICATIONS: Essential or symptomatic Asthma, Broncho-pulmonary or cardio-vascular dyspnoeic affections, Dyspnoea of Emphysema.

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Tablets—Tin of 30	3/5½, plus 1/- purchase tax
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Sample and literature to the Medical Profession on request

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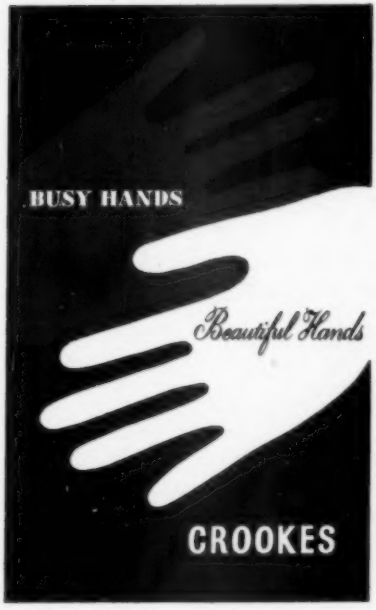
Sole Concessionaires: BENGUE & CO. LTD. *Manufg. Chemists*
MOUNT PLEASANT, ALPERTON, WEMBLEY, MIDDX.



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HAND LOTION: 2 oz. bottle 2/9½d. inc. P. Tax
4 oz. bottle 3/11d. inc. P. Tax

Hand Cream & Lotion

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FOR NERVOUS AND MENTAL DISORDERS

President—THE EARL SPENCER

Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

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The seaside house of St. Andrews Hospital is beautifully situated in a Park of 330 acres, at Llanfairfechan amidst the finest scenery in North Wales. On the north-west side of the Estate a mile of sea coast forms the boundary. Patients may visit this branch for a short seaside change, or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout fishing in the park.

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3¾% TAX FREE

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A New M.M.P. Product

EFFECTIVE NON-BARBITURATE SEDATION

★ Each tablet contains :

Mephenesin	200 mg.
Carbromal	200 mg.
Bromvaletone	70 mg.
Ascorbic Acid	30 mg.

Professional Sample and Literature gladly available on request.

Available in bottles of 50 tablets.

Prescribable on N.H.S. Form E.C.10.

Growing recognition of the long-term cumulative toxic effects of barbiturates, and the well-known, insidious, psychic habituation to their use—matters of considerable concern to many Doctors—are now avoidable dangers through the formulation of Noctynol Tablets. The latter present :

MEPHENESIN, which, by diminishing reflex hyper-excitability, relieving nervous tension and anxiety, and promoting muscular relaxation, not only induces the composure essential to the onset of sleep, but also ensures that the sleep is restful and refreshing.

CARBROMAL and BROMVALETONE which, by synergism, act as effective hypnotics and quickly transform the mephenesin-induced sedation to hypnosis. Unlike the barbiturates, carbromal and bromvaletone are non-toxic and non-cumulative and, as elimination is comparatively rapid, they rarely give rise to 'hang-over' and depression.

In smaller doses, NOCTYNOL Tablets act as a non-depressant calmative eminently suitable for daytime sedation.

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Successful Clinical Practice spreading over many years is proof of the trustworthiness of THE ORIGINAL PRODUCT. Standard works on cardiology and current medical literature contain numerous references to the unfailing reliability and constant activity of NATIVELLE'S DIGITALINE. Literature and samples will gladly be forwarded on request.

Supplied in the following stable forms:—

TABLETS (PINK) 0.1 mg. = 1/600 gr. TABLETS (WHITE) 0.25 mg. = 1/240 gr.
AMPOULES for intramuscular and intravenous injection 0.20 mg. = 1/300 gr.
Digitaline Tablets now available in dispensing packs of 200.

NATISEDINE
Tablets of 0.10 gm. of phenylethylbarbiturate of quinidine.
Bottles of 20 and 100 tablets.

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Dragées of Nitroglycerine.
Boxes of 40.

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International Standard of Ouabaine kept in National Institute for Medical Research, London.

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All forms of Nativelle's Digitaline & Ouabaine Arnaud are exempt from Purchase Tax.

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"EUPINAL"

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Asthma and Chronic Bronchitis

and may be prescribed on N.H.S. Form E.C.10

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In chronic Bronchitis "Eupinal" softens the tough accumulated mucus in the bronchial tubes and allows it to be more readily expectorated. In Asthma it possesses a more markedly soothing effect, lessening the frequency of attacks and reducing their severity and duration, and relieving breathlessness. "EUPINAL" contains no poison and is safe in use.

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The safest and best preparation of opium

Nepenthe contains all the constituents of opium and has been prescribed for over 100 years. It has been found by generations of Practitioners to be the best preparation of Opium as it does not cause the unpleasant after-effects usually attributed to opiates. It can be given over a considerable period and the effect remains invariably constant.

Packed in 2-oz., 4-oz., 8-oz. and 16-oz. bottles and for injection in ½-oz. rubber-capped bottles, sterile, ready for use.

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FERRIS & CO LTD

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Telephone 21381 *Telegrams FERRIS BRISTOL*

for the ulcerated leg...

LESTREFLEX

DALMAS Elastic Diachylon Bandage ventilated is the ideal emolient strapping and is non-rubberised. It gives efficient adhesion and yet causes minimal sensitivity reactions. It is "the" strapping for the pressure bandaging treatment of oedematous, eczematous or ulcerated legs. Ventilated Lestreflex is available in 3 yard rolls. 3" and 4" wide. The Lestreflex Bandage is a REMEDY par excellence for this problem!

M6

DALMAS ELASTIC DIACHYLON BANDAGE

℞ VENTILATED LESTREFLEX

available on E.C.10

Descriptive literature is available from the manufacturers

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ASTHMA

Instant relief!

Ever increasing numbers of medical men are relying on Rybarvin Inhalant to combat bronchospasm. The Ministry of Health having agreed to the prices of Rybar asthma inhalants, Rybarvin can be freely prescribed.

RYBARVIN brings relief. Consistently, often spectacularly, attacks are cut short and their frequency lesssened. Free from excess acid, non-irritant and non-habit-forming it is an ideal inhalant for all asthmatics young and old.

RYBAR INHALER has been specially designed for aerosol therapy.

Other RYBAR Products for asthma include **RYBAREX** Inhalant for cases complicated by Bronchitis and **RYBRONSOL** Powder, an ideal sedative. All, including the Inhaler, may be prescribed on N.H.S. Form E.C.10.

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Rybarvin Formula

Pituitary Extract. Posterior and Anterior Lobe	0·40% w/v
Methylatropine Nitrate	0·14% w/v
Papaverine	0·08% w/v
Adrenaline	0·40% w/v
Ethyl Para-aminobenzoate	0·20% w/v
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PB 15

Who's next?

Another rheumatic sufferer?

It is fortunate that an effective adjuvant in the treatment of this disease is available, bringing the patient prompt and effective relief from pain.

The value of salicylate in rheumatic disorders has long been recognised, but until recently its use was restricted by the toxic effects accompanying the necessarily high dosage.

In Berex, the combination of acetylsalicylic acid and calcium succinate enables toleration of massive aspirin dosage without lowering the prothrombin level, with encouragement of tissue respiration, and with less gastric disturbance.

BEREX ***has never been advertised to the public.***

SUMMARY OF STUDY ON SUCCINATE-SALICYLATE THERAPY*

A succinate-salicylate combination was found superior to acetylsalicylic acid in rheumatic states both on grounds of therapeutic efficacy and lower toxicity. Adequate amounts of the former could be administered with more lasting effect and with fewer and milder side effects. Furthermore, succinate - salicylate affects the disease process itself, as well as relieving painful symptoms and does not abnormally increase prothrombin time even after prolonged dosage.

* *Delaware State Medical Journal* (1954) 26, 22.

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SUCCINATE-SALICYLATE THERAPY

For the relief of the painful symptoms associated with all rheumatic disorders

FORMULA: *Calcium Succinate* 2.8 *gr.* *Acetylsalicylic Acid* 3.7 *gr.*

IN TABLET FORM: *Basic N.H.S. Price* 4/8½*d.*—100 *tablets;* 24/3*d.*—600 *tablets.*

A professional sample will be gladly sent on request to

MEDICAL DEPARTMENT

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'I think it's my nerves, doctor' It has been calculated that 2 in 6 prescriptions under the NHS are for 'nerves'*. These patients, who may present with a bewildering variety of vague non-organic signs and symptoms, all have one thing in common—they worry too much. Since this lessens their ability to deal with routine problems a vicious spiral of increasing worry and decreasing competence is set up.

Combined with a doctor's advice and reassurance 'Drinamyl' gives these patients a holiday from tension. By inducing a mood of cheerful calmness, without drowsiness or inappropriate euphoria, it enables them to take a fresh look at their situation. Imaginary worries are set aside and energy sensibly apportioned to deal with matters of real concern.

'Drinamyl'
for the harassed patient

Available for prescription in containers of 100 *tablets*
'Drinamyl' is also available in 'Spansule' brand sustained release capsules

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DLP 26 (Col)

**Quoted in Lancet* (1955 *i*, 14)

How to stop between-meal eating

'Dexedrine Spansule' sustained release capsules –
the new way of controlling appetite in weight reduction –
curb the appetite *between meals* as well as at mealtimes.
This is because each 'Dexedrine Spansule' capsule releases
the medication evenly over an 8 to 10 hour period,
providing effective appetite control that lasts all day.
Available in containers of 30 capsules,
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FULLY DESCRIPTIVE literature is available and a Technical Information Service is always at your disposal.

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Cheyne-Stokes Respiration

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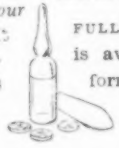
A CLEAR CASE FOR CARDOPHYLIN. Best known and most widely used of the purine derivatives, Cardophylin is the one drug which combines *four* methods of treating heart failure. It is a respiratory stimulant; it controls bronchospasm; it increases coronary flow; and it is a diuretic.



IT IS PRESENTED in tablets, suppositories, and ampoules for intravenous and intramuscular administration.

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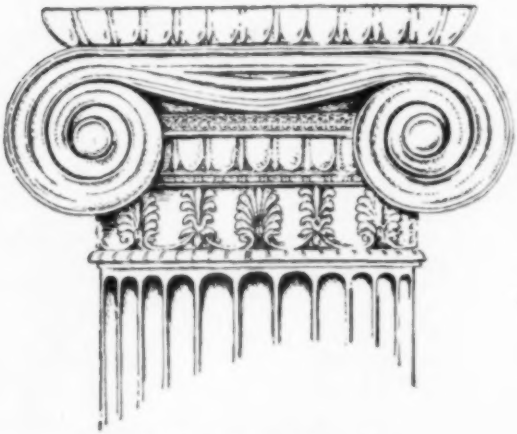

FIVE YEARS' PROVEN EFFECTIVENESS

in general practice

Over five years' usage in general medical practice throughout the world has established Chloromycetin* as today's foremost broad spectrum antibiotic. Chloromycetin is unrivalled for the effectiveness and rapidity with which it is absorbed following oral dosage. This coupled with its outstanding tissue diffusibility, results in swift, consistent clinical response and provides the flexibility of treatment desirable for varying conditions. Development of resistance by the common pathogens during Chloromycetin therapy is extremely rare and the facility with which it is absorbed accounts for the low incidence of gastro-intestinal upset.

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THE ORIGINAL CHLORAMPHENICOL

CHLOROMYCETIN CAPSULES · SUSPENSION CHLOROMYCETIN PALMITATE
Chloromycetin Ophthalmic · *Chloromycetin Ophthalmic Ointment*
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Hæmorrhoidal Ointment
Prescribable on E.C.10

For the treatment of hæmorrhoids, pruritus ani and painful inflammatory and eczematous lesions of the skin in the anal region.

HEMATRIX is designed for the immediate relief of itching and localised pain through progressive treatment of the enlarged and varicose tissues by mild antacid astringent action.

HEMATRIX acts promptly, effectively and thoroughly, promoting the disappearance of subjective symptoms.

HEMATRIX contains as active ingredients: Benzocaine 6%. Alum. Oxide 7.5%, Zinc Oxide 15%. Bals. Peruv. 2.5%, in a suitable emollient vehicle. Presented in tubes complete with extension introducer for internal application.

Maw's Ethical Products also include

NAPHTHIONIN A hæmostatic of general action for administration by the parenteral route; used pre-operatively or post-operatively. Naphthionin does not control hæmophiliac bleeding for which Thrombin (MAW) is the hæmostatic of choice.

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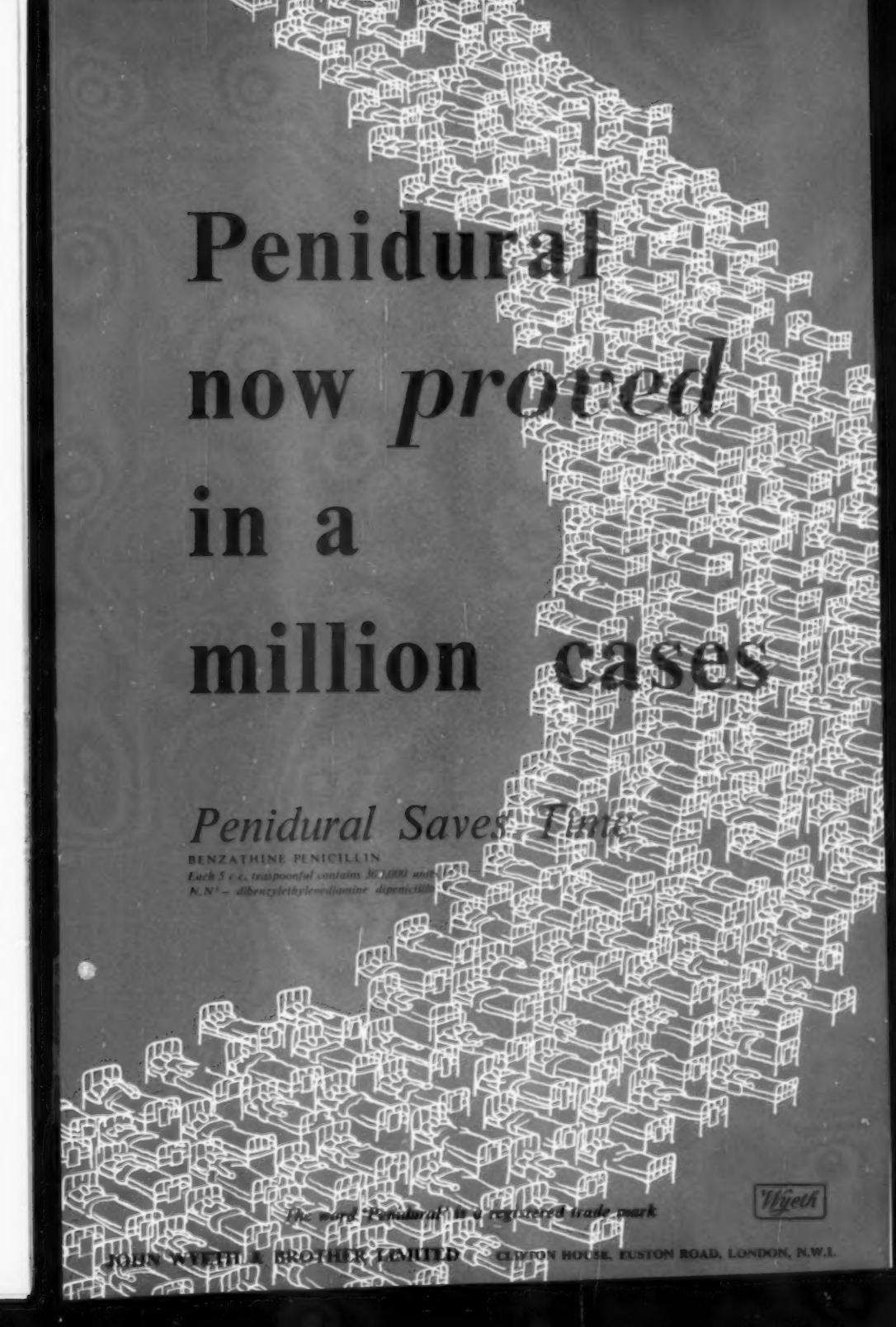
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Save time on urine tests with . . .

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Reagent Tablets
for the detection of Glycosuria

Reagent Tablets
for the detection of Ketonuria

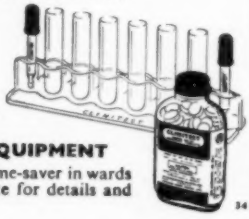
Both tests performed simultaneously in 1 minute!

Specialists, General Practitioners, Clinics and Hospitals in all parts of the country have used and prescribed 'Clinitest' Reagent Tablets since 1947. Many valuable hours have been saved. Now after intensive research work and clinical trials the makers of 'Clinitest' Reagent Tablets have produced 'Acetest' Reagent Tablets for the detection of Ketonuria. With 'Clinitest' and 'Acetest' Reagent Tablets, reliable routine sugar and acetone tests can be carried out *simultaneously* in one minute!

CLINITEST

No external heating • No measuring of reagents

Approved by the Medical Advisory Committee of the Diabetic Association. The 'Clinitest' set, refills and accessories are all available under the N.H.S. on Form E.C.10. *(Basic Drug Tariff Prices: Set 6/8 complete. Refill bottle of 36 tablets 2/4.)*



CLINITEST HOSPITAL EQUIPMENT

An invaluable time-saver in wards and clinics. Write for details and hospital prices.

34

The advantages of

ACETEST

Reagent Tablets

Quick and reliable, a single tablet provides all the reagents to perform a test. Low cost permits this tablet test to be used as a screening procedure or as a routine for diabetic patients. No danger of false positives with normal urine No caustic reagents.

TO PERFORM A TEST:

1 Put 1 drop of urine on tablet.
2 Take reading at 30 seconds. Compare tablet to colour chart provided.
3 Record results as negative, trace, moderate or strongly positive.

Supplied in bottles of 100 tablets with colour scale.

'Acetest' Reagent Tablets *(diagnostic nitroprusside tabs.)* are also available under the N.H.S. on Form E.C.10. Basic Drug Tariff price 3/10 per bottle of 100 tablets (with colour scale).

REFERENCES

(1954) 'Clinical Tests for Ketonuria', *'Lancet' April 17th, pp.* 801/804

(1954) '*Medicine Illustrated*', *May, p.* 289

(1954) '*Practical Clinical Biochemistry*', *Heinemann, p.* 74

(1954) 'Clinical Tests for Ketonuria', *'Lancet', July 10th, p.* 95

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Simple, effective contraception

where secondary occlusive methods are unacceptable or impracticable

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Ortho

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"Versatile stuff, aspirin—
I see the rheumatism boys
now say it's as good as cortisone."

*"Yes, but nobody yet seems
to know how it works
or even its site of action."*

"Some professor suggested
the analgesic effect of salicylates
might be peripheral," at tissue level,
not central as we were taught."

*"Could be. That reminds me—some firm has put up a new
skin-penetrating salicylate in a vanishing cream
for local tissue pain by inunction."*

"Does it work? And isn't it irritating?"

*"Yes and no. I've used it and it works well,
even in osteoarthritis. It's not irritating at all,
just a means of using salicylate locally."*

"Sounds promising. I'd like to try it. What is it called?"

* Practitioner, 170, 515 (1953)

Algesal

10% diethylamine salicylate in a soothing vanishing cream

**non-irritant, skin penetrating salicylate
for the relief of rheumatic pain by inunction**

Full literature and samples gladly sent on request to the manufacturers:
E. G. H. LABORATORIES LTD. PERU STREET, SALFORD 3, LANCS.

Sebbix

CREAM

A safe treatment containing 2% salicylic acid, 3% sulphur and purified fractions equivalent to 10% crude coal tar in a water miscible base. Sebbix is non-greasy, virtually odourless and is readily used by female patients since it does not mat or clog the hair. Prescribable on E.C. 10. Basic N.H.S. cost per 1 oz tube 2/3.

Sebbix shampoo

A stimulant and antiseptic preparation which quickly controls dandruff while being an ideal shampoo for routine use. Contains purified fraction equivalent to 2% coal tar with 1% hexachlorophene in a soapless shampoo base. Not generally prescribable on E.C. 10, but a bottle sufficient for 6 to 8 good shampoos is only 3/3.

for

psoriasis of the scalp

seborrhoea

dandruff

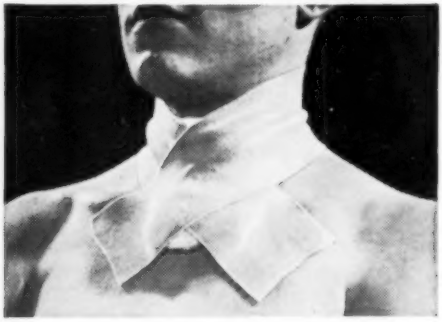
GENATOSAN LTD. *Loughborough, Leicestershire.*

Elastoplast Bandaging Technique

in the treatment of

Post-Operative Conditions

SURGERY is a field in which Elastoplast elastic adhesive bandages are widely used with marked success. The illustration shows the 'stole' method of applying Elastoplast to the neck after operation in that region, e.g. thyroidectomy. It is an efficient method of retaining dressings in position and saves time, trouble and discomfort to the patient.



SOME OF THE MANY OTHER USES OF ELASTOPLAST IN MEDICAL PRACTICE

To reduce umbilical and inguinal hernia in children

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To retain a dressing in position on the head

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Compression treatment of leg ulcers

Support, and control of effusion, in joint injuries

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Fixation of empyema tubes, catheters and intravenous drips

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To close the edges of a gaping wound

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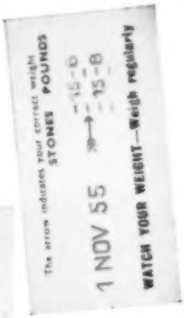

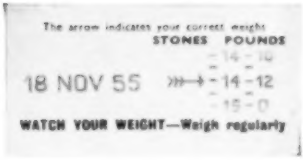

PRELUDIN*

the Appetite Controlling Agent that is Safe even in Cardiovascular Disorders

PRELUDIN is new and PRELUDIN is news because it provides a new practical answer to an old problem. Here for the first time is a treatment for obesity that is safe, swift and sure for *all* patients—and particularly for those with cardiovascular disorders and hypertension.

PRELUDIN is an appetite controlling agent. It acts quickly and effectively without risk by controlling the patient's appetite and breaking the psychogenic overeating habit, thus curbing food intake. It enables the patient to lose weight safely and without mental strain by strengthening adherence to a prescribed diet.

PRELUDIN, in recommended dosage, unlike dexamphetamine, does *not* raise the blood pressure, does *not* affect the heart, and does *not* create excessive mental stimulation. It is the prescription of choice in *all* cases of obesity—especially those with cardiovascular disorders—because it reduces the risk of reducing.

PRELUDIN

brand of 2-phenyl-3-methyl-tetrahydro-1,4-oxazine-hydrochloride

—the safe prescription for obesity

INGELHEIM

Manufactured and distributed in England by Pfizer Ltd., for C. H. Boehringer Sohn, Ingelheim am Rhein, Registered proprietors of the trade mark. **Regd. Trade Mark*

A New Sandoz Hypnotic

and Sedative . . .

PLEXONAL

The combination of dihydroergotamine and hyoscine with sub-threshold doses of 3 barbiturates is a new solution to the difficult problem of inducing sleep and general sedation without any side or after effects.

Composition

Each tablet of Plexonal contains:
0.16 mg. dihydroergotamine methanesulphonate,
0.08 mg. hyoscine hydrochloride,
45 mg. barbitone sodium,
15 mg. phenobarbitone sodium,
25 mg. sodium isobutylallylbarbiturate.

Dosage

One to three tablets as required

Packages

Tubes of 20 and 200 tablets

Literature and samples available on request

SANDOZ

SANDOZ PRODUCTS LIMITED

134, Wigmore Street, London, W.1

Between the 'up' and the 'about'

Serious illness is inevitably followed by a frustrating period of convalescence. Metatone,* with its stimulating, appetite-promoting combination of vitamin B_1 with strychnine and mineral glycerophosphates is ideally suited for the rapid restoration of normal metabolic function. It is specially valuable after 'flu and similar debilitating illnesses, after surgical operations, in neurasthenia and during pregnancy and lactation.

FORMULA
Each fluid ounce of Metatone contains:

Vitamin B_1	3 mg.
Calcium Glycerophosphate	4 gr.
Potassium Glycerophosphate	4 gr.
Sodium Glycerophosphate	2 gr.
Manganese Glycerophosphate	½ gr.
Strychnine Glycerophosphate	8/200 gr.

METATONE

*Trade Mark

Parke, Davis & Co. Ltd., (*Inc. U.S.A.*) HOUNSLOW, MIDDLESEX
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A New

ASTHMA THERAPY

SPEEDY AND LONG LASTING ACTION COMBINED

The "two-phase" therapy provided by ISO-BRONCHISAN sets new standards of efficiency in asthma control. Outer layer of the tablets consists of Isopropyl-Nor-Adrenaline—a potent bronchodilator well absorbed by the sublingual route. When the tablet is placed under the tongue, this layer dissolves and symptoms are *promptly* relieved. Swallowing of the tablet's nucleus presents its content of Ephedrine and Theophylline for slow absorption by the alimentary route—so maintaining and *prolonging* the antispasmodic action on the bronchial smooth muscle.

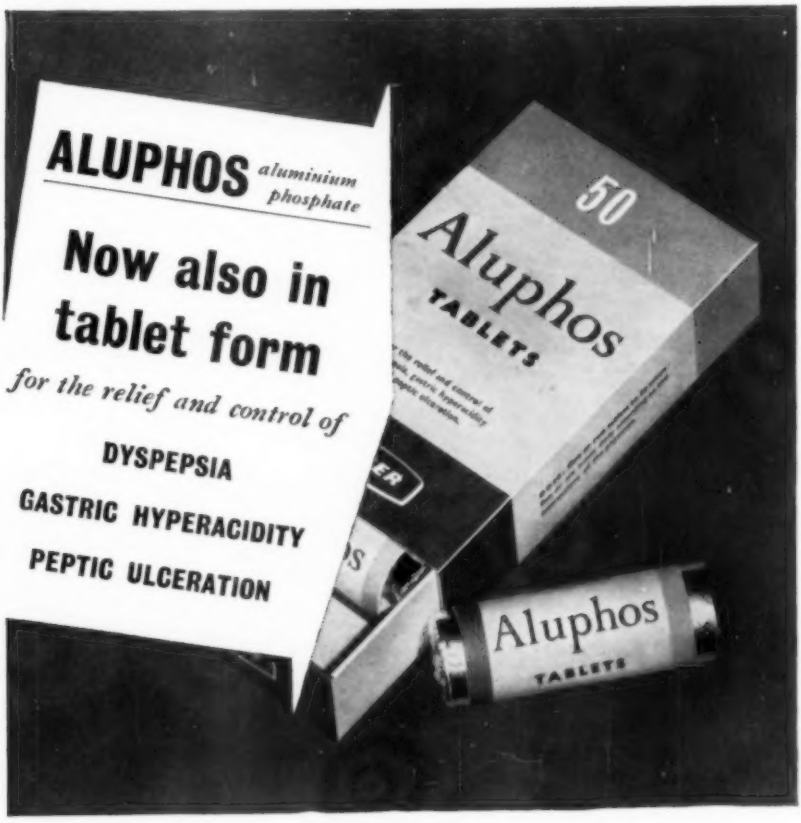
Each tablet contains Isopropyl-Nor-Adrenaline (Isoprenaline) sulphate gr. ¼; Ephedrine hydrochlor gr. 2/5; Theophylline gr. 2. In tubes of 20 tablets and bottles of 100 tablets.

SILTEN

ISO - BRONCHISAN

Prescribable on Form E.C. 10

Silten Limited • Silten House • Hatfield • Herts • England



New Aluphos tablets offer all the advantages of Aluphos gel—in convenient portable form. Aluphos tablets are non-constipating. They do not interfere with the absorption of phosphate or vitamins from the gut. Aluphos tablets are free from grittiness and pleasantly flavoured. Each Aluphos tablet is therapeutically equivalent to one teaspoonful of Aluphos gel.

Presentation Packed in boxes containing 5 rolls of 10 tablets each.

A BENGER PRODUCT **Aluphos** (TRADE MARK)

m/1

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE

INTERNATIONAL STANDARD FOR HYALURONIDASE

An international standard for preparations of hyaluronidase has been established (World Health Organisation, Geneva, October 1955).

Hyalase—the first British preparation of hyaluronidase—was developed by Benger Laboratories and, in the absence of international agreement, a "Benger" unit was adopted and became widely accepted.

The strength of Benger 'Hyalase' ampoules remains unchanged (1000 Benger units) but will in future be decribed in terms of the new international unit.

Each ampoule of Hyalase contains 1500 international units.

HYALASE

Hyaluronidase

Hyalase ampoules (1500 international units) are available in boxes of 5, 20 and 100.

A PRODUCT OF BENGER RESEARCH

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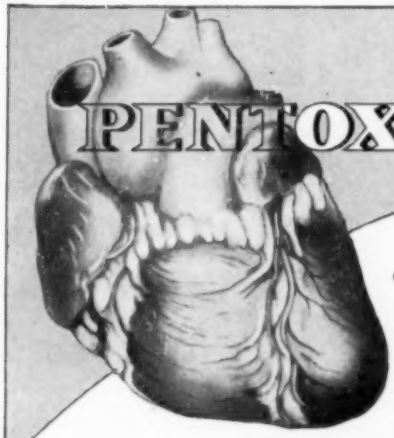

PENTOXYLON

... the new therapy

for

Angina Pectoris

In 'Pentoxylon' the tranquillizing, bradycardic influence of 'Rauwiloid' brand alkaloid hydrochlorides of Rauwolfia serpentina is allied to the prolonged vasodilating effect of pentaerythritol tetranitrate. This new combined therapy represents an important advance in the long term treatment of angina pectoris.

Although some patients will still occasionally require glyceryl trinitrate, in many others 'Pentoxylon' will provide complete relief from anginal attacks. It will also bring: "*gratifying reduction of anxiety and relief of apprehension . . .*"

North-West Med. (1955) 54: 34

Dose: 1 tablet four times a day, before meals, increased later if necessary.

RIKER

'Pentoxylon' is available in tablets, each containing 1 mg. of 'Rauwiloid' and 10 mg. of pentaerythritol tetranitrate, available in bottles of 25, 100 and 500.

'RAUWILOID' and 'PENTOXYLON' are registered trademarks
Registered Users:

RIKER LABORATORIES LIMITED
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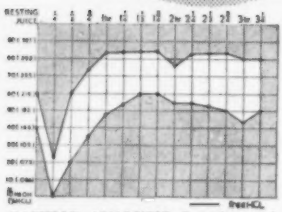
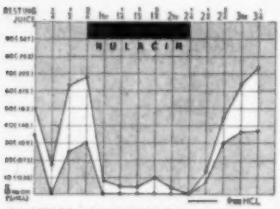
Drip therapy without a tube

NULACIN



GASTRIC ANALYSIS Superimposed gruel fractional test-meal curves of five cases of duodenal ulcer



GASTRIC ANALYSIS Same patients as in Fig. 1, two days later, showing the striking neutralizing effect of sucking Nulacin tablets (3 an hour). Note the return of acidity when Nulacin is discontinued.

In the past, the successful treatment of many cases of peptic ulceration demanded hospital conditions. Now, by means of Nulacin Tablets, it is possible to control gastric hyperacidity without any inconvenience to the patient. By using Nulacin Tablets as directed, an ambulant patient can obtain all the advantages of intragastric milk-alkali drip therapy.

INDICATIONS

NULACIN tablets are indicated whenever neutralization of the gastric contents is required: in active and quiescent peptic ulcer, gastritis, gastric hyperacidity.

Beginning half-an-hour after food, a NULACIN tablet should be placed in the mouth and allowed to dissolve slowly. During the stage of ulcer activity, up to three tablets an hour may be required. For follow-up treatment, the suggested dosage is one or two tablets between meals.

NULACIN tablets are not advertised to the public, have no B.P. equivalent, and may be prescribed on E.C.10. The dispensing pack of 25 tablets is free of Purchase Tax. (Price to pharmacists is 2/-.) Also available in tubes of 12.

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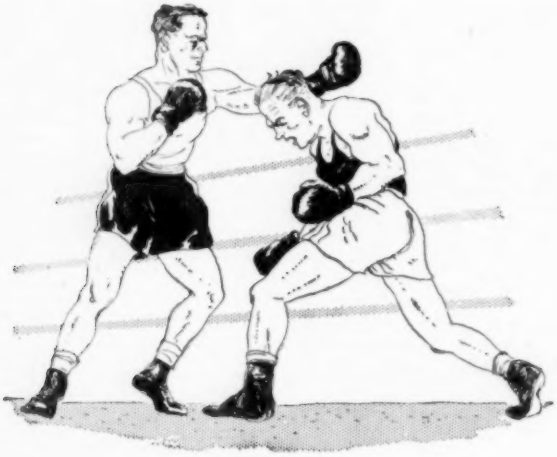

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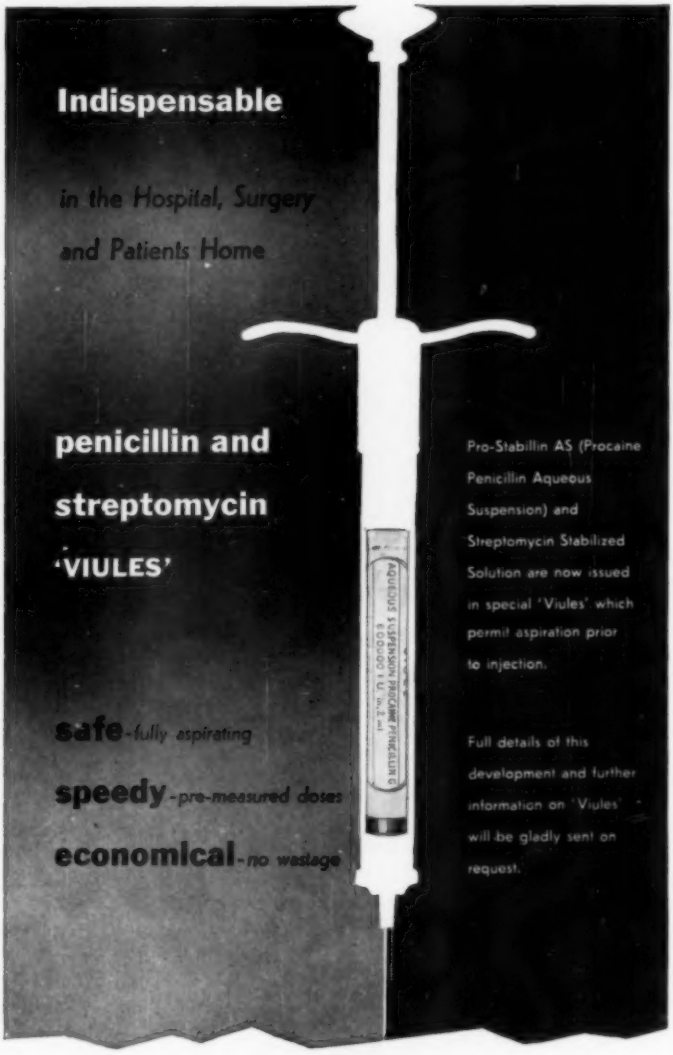
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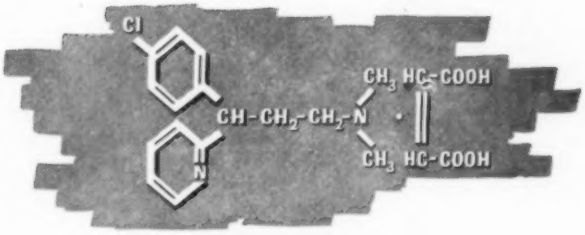

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REFERENCES
Practitioner, 173: 46, 1954 Brit. Med. J., 2: 7, 1955.
Ibid., Editorial, 2: 31, 1955.

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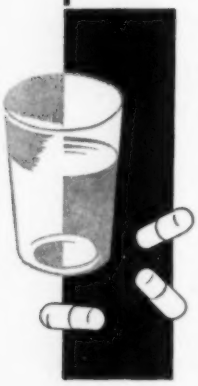

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THE PRACTITIONER

No. 1051 JANUARY 1956 Volume 176

THE MONTH

The Symposium

DURING the last twelve years some 3,500 antibiotics have been isolated. Seventeen of these are now in commercial production, and at the third annual symposium on antibiotics held in Washington in November another dozen were under review. For the clinician this embarrassment of riches has raised almost as many problems as it has solved. In the first place, which is the antibiotic of choice in any given case? Secondly, what is the toxicity of a given antibiotic? Thirdly, and perhaps most important of all, what effect is the indiscriminate use of antibiotics having upon the natural immunity processes of our patients? These are some of the problems which are dealt with in our symposium this month. Last January we devoted a symposium to penicillin, the first, and, curiously enough, still the safest and most generally useful antibiotic of all. This month we review the other nine antibiotics in general use.

In this symposium, read in conjunction with our symposium on penicillin, the practitioner will find the answer to the problems of the choice of antibiotic and of toxicity. It may be complained that our contributors have laid undue emphasis upon the harmful effects of these potent weapons in the fight against infection. Such an emphasis, however, is clearly indicated at the present moment, if only to counteract the over-enthusiastic claims which tend to be made for each new antibiotic as it appears on the therapeutic horizon. 'Après nous le déluge' is a Pompadourian philosophy which has no place in the practice of medicine. The exceptional safety of penicillin put us off our guard. The impression was created that antibiotic therapy could be applied with impunity. Time has shown that this is not so. Not a single antibiotic introduced subsequent to penicillin has rivalled it in non-toxicity.

But perhaps the most important problem of all is the effect which the use of antibiotics is having upon the natural immunity processes of the body. There is no difficulty about the clear-cut indications for antibiotics. The patient with pneumonia, typhoid fever, subacute bacterial endocarditis, meningitis, or septicæmia must be given the appropriate antibiotic forthwith and in full doses. But what justification is there for the indiscriminate use of antibiotics in those minor infections of life to which we are all subject? Have we forgotten that Nature can deal with many of these infections,

and deal with them much more effectively, though possibly less expeditiously, than we can with antibiotics? The antibiotics may, and often do, knock out the infecting organism very rapidly, but in so doing they deprive the patient of that immunity from subsequent infection which he would have acquired if the infection had been allowed to run its course. Further, by this wholesale and uncalled-for use of antibiotics the practitioner is exposing his patients to the not inconsiderable risk of rendering them vulnerable to a subsequent and more serious infection as a result of having either induced hypersensitivity to the antibiotic or rendered the causative organism resistant to the antibiotic.

If the community is to obtain the full benefit of the tremendous advantages bestowed upon humanity by the discovery and development of antibiotics, it is essential that these preparations should be used correctly and with circumspection. Only if the clinician exercises 'eternal vigilance' will his patients reap the full benefit of the antibiotic harvest.

G.P. Consultants

EARLY in 1954, following a long debate in the Northern Ireland House of Commons, the Northern Ireland Hospitals Authority set up a special committee to consider the criticisms raised in this debate and to advise the Authority on the steps which should be taken to improve the efficiency of the Health Service. The report of this committee, which is included in the recently published seventh annual report of the Authority, is deserving of the most careful attention of all who are concerned with the maintenance of professional freedom in a nationalized service. Perhaps the committee's most interesting recommendation is that 'the Authority should not exclude the possibility of a person undertaking duties as consultant and maintaining a general practice'. It is admitted that this could not apply to the more highly specialized branches of medicine and surgery but, in the committee's opinion, 'there can be no doubt that if a general practitioner has the necessary training and qualifications there are a great many branches of hospital work in which he could participate on level terms with those who devote their whole time to that work': e.g. pædiatrics, geriatrics, dermatology, anæsthetics, ophthalmology, and obstetrics.

This is a welcome challenge to the current trend to over-specialization. It is obviously a most revolting suggestion to the bureaucratic mind which must have everything categorized and classified. To such the mere suggestion of such a monstrosity as a general-practitioner-consultant is anathema. To the clinician, however, the recommendation is like a breath of fresh air in the hot-house atmosphere of high-power administration in which the medical services have wilted during the last seven years. It is not every general practitioner who will want to add consulting work to his duties, even if he has the ability. But there is no good reason why those who wish to do so, and have the ability, should not undertake the double function. Apart from anything else, it is along these lines that lies a

solution to the current problem of the registrar who is unable to obtain a consultant appointment under present conditions.

Heroin

THE ban on heroin has been raised. Even though the right decision has been taken for the wrong reason, there will be general relief in the profession that those practitioners who consider heroin to be the drug of choice in selected cases will be able to abide by their clinical judgment. The Minister of Health and his advisers have laid themselves open to severe criticism in their handling of this affair, and it is to be hoped that all practitioners who value professional freedom and practise according to the tenets of the Hippocratic Oath will take due notice of the threat involved in this attempt by a Minister of State to ban the use of an established drug. It is one of the freaks of fortune that it should have been a Government of the present political complexion that took this retrograde step. No-one questions the necessity for this country making a contribution towards the international control of drugs of addiction, but this was not the way to do it. As Dame Rachel Crowdy-Thornhill, who as Dame Rachel Crowdy was for long the League of Nations authority on the subject, has pointed out, 'It is international control and not prohibition which lessened the illicit traffic in habit-forming drugs'.

The implications of this unfortunate affair are far-reaching, and we trust that they will receive the serious consideration of every member of the profession. Whatever the Minister and his advisers may say, the right of a doctor to do what he considers best for his patients has been challenged. If this can happen once, and with a Conservative Government in power, it can happen again. Specious speeches about the importance of family doctors are no safeguard against a whole-time nationalized medical service with Government edicts instructing doctors how to treat their patients. This is the spectre which must haunt every practitioner as he watches developments in the National Health Service.

TV and Postgraduate Education

'TELEVISION can come to play a significant role in postgraduate medical education', according to a survey of postgraduate medical education in the United States recently published by the American Medical Association ('Postgraduate medical education in the United States', by Douglas D. Vollan, M.D.). This is an aspect of postgraduate education which has received considerable attention in the United States of recent years. The earliest experiments consisted of short telecasts of surgical procedures as novelty features during large medical society meetings. Late in 1953, the first organized postgraduate programme by television was broadcast from a central source to a number of cities in the Eastern States. Reception, however, was only possible by groups with a closed-circuit system and there was little saving in time for the participating practitioners as they had to travel to and from the centres where the telecasts were received.

Obviously, the greatest value of television is in bringing instruction from medical centres directly into the home of the practitioner. This means the use of open circuits, and here the difficulty is preventing the telecasts being received by the general public. One means of overcoming this is to use morning hours earlier than the public are accustomed to expect the station to be operating. This method was tried out in 1953, when a postgraduate programme was broadcast in one area on an open circuit, the doctors in the area having been notified by post of the date and time of the telecast. A more effective way of restricting such programmes to those for whom they are intended is by means of 'scrambling'. By the use of an electric code card or other method it is possible to limit the viewing of any programme to those who have the unscrambling device and who have also the 'key' to the particular programme involved. This method has actually been used experimentally in New York, but there are considerable technical difficulties to be overcome before it can be developed on anything like a large scale. The American Medical Association, however, considers that this may well be 'a feature of major significance in postgraduate medical education'.

A Tax on Knowledge

THE drastic increase in postal charges which comes into force today (January 1) is a serious blow to the dissemination of knowledge. As the distinguished members of the National Book League have pointed out in a letter to *The Times*, 'the tragic results' of the virtual doubling of postal charges on periodicals and books, which is involved in the new rates, will mean that 'Great Britain will stand alone among the civilized countries of the world as having completed an entirely retrograde step'. In our own case the increase will involve us in an additional expenditure of well over £3000 a year. The increased charges are not only 'tragic', but also grossly anomalous. The concession rate for newspapers is still retained, but no journal is accepted in the G.P.O. register of newspapers unless it is published at least weekly. This means that as from today the postage will be virtually doubled on medical, scientific and literary journals which are published monthly or quarterly, as well as books, but any periodical, such as comics—horror or otherwise—which is published at least weekly will not be charged anything extra. We trust that the Government will have second thoughts before it takes this step of imposing what will virtually be a tax on knowledge.

In spite of this grossly unfair imposition we do not intend to increase our subscription rate. There can be few journals in this country—with the notable exception of *Punch*—which can emulate our record of not having raised the subscription rate since 1917. On more than one occasion we have been informed by readers that they would be quite prepared to pay more. Whilst we appreciate the compliment, we realize the financial stringency imposed upon doctors, as on all the professional classes, by the increase in cost of living, including mounting subscriptions to medical societies. Our aim therefore will be to maintain the subscription rate at its present level.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

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In assessing the present status of streptomycin and dihydrostreptomycin it is necessary to consider first the two outstanding limitations which they share: the rapidity with which many bacteria become resistant and the dangers which accompany their use. For practical purposes the streptomycins differ in their effects only in regard to the damage which may be done to the eighth cranial nerve. This, however, has proved to be all important in determining the relative merits of the two antibiotics.

BACTERIAL SPECTRUM

Initially many bacteria are sensitive to streptomycin, which in high concentrations is bactericidal and in lower concentrations is bacteriostatic. Some bacteria are resistant from the outset and a few may even have their growth stimulated by streptomycin. An organism which is sensitive may rapidly become resistant in the presence of the antibiotic. This occurs in one step by a genetic mutation causing sufficient biochemical modification of the bacterial cell to render it invulnerable to concentrations of streptomycin many hundred times in excess of that to which the organism was originally sensitive. This is in contrast to the multistep method by which organisms may slowly become resistant to penicillin over long periods of time, as has occurred in the case of the staphylococcus. Unfortunately, resistance to streptomycin means that the organism is also resistant to dihydrostreptomycin and vice versa. The most effective method of preventing the development of resistance is by the simultaneous administration of a second chemotherapeutic agent to which the organism is also sensitive. The chances of the bacterial cell undergoing the twofold mutation necessary for its protection diminish significantly. Even so the facility with which organisms acquire resistance seriously limits the usefulness of the streptomycins.

Although many gram-positive organisms are sensitive to streptomycin it is seldom called for in a sphere in which penicillin is supreme. It has been demonstrated both clinically and experimentally, however, that the simultaneous administration of penicillin and streptomycin has a synergistic effect. Thus, the two antibiotics may be given together with advantage in infections relatively insensitive to both.

In many instances of infection due to gram-negative organisms the tetracyclines and chloramphenicol have superseded streptomcyin but when the broader spectrum antibiotics are relatively ineffective or contraindicated streptomycin has a limited part to play. In Great Britain the most important

gram-negative organisms for which streptomycin may be required are *H. influenzæ*, *Klebsiella pneumoniæ* (Friedländer's pneumobacillus), *Brucella abortus* and some strains of *E. coli*, *Proteus and Pseudomonas*. *Pasteurella pestis* and *Pasteurella tularensis* are also highly sensitive to streptomycin.

It is of course in tuberculosis that streptomycin, in conjunction with other chemotherapy, has an outstanding importance. In recent years the use of streptomycin in the treatment of tuberculosis has steadily increased whilst its employment in other infections has diminished.

ADVERSE EFFECTS

The principal adverse effects of the streptomycins are ototoxicity, hypersensitivity, certain serious but rare reactions and a miscellaneous group of minor troubles.

Ototoxicity.—In the early days of its use the dosage of streptomycin was appreciably higher than at present and in these circumstances vestibular damage and, to a lesser extent, deafness were common. The severity and frequency of ototoxicity increase with the size of the dose and the duration of treatment. Nowadays, with smaller doses these toxic effects are much less often encountered. In the case of dihydrostreptomycin, deafness, the onset of which may be delayed, is more prominent than vertigo. Even with a daily dose of 1 g. of dihydrostreptomycin serious impairment of hearing is comparatively common after prolonged administration. The first indications of ototoxicity with either drug are high-tone (audiometric) loss or sustained high-pitched tinnitus. A young person may be able to compensate for vestibular damage but deafness tends to be progressive and permanent. The elderly and those with impaired renal function stand in greatest danger. Streptomycin is therefore to be preferred to dihydrostreptomycin. When prolonged treatment is necessary vestibular damage can be held to a minimum if the daily dose does not exceed one gramme. By combining streptomycin and dihydrostreptomycin in equal quantities and using the same total of this combination as of either of the drugs singly, the risk of damage to the eighth nerve is still further decreased without apparent loss of therapeutic effect. The risk of impairment of hearing is not eliminated, however, (Lumsden, 1953) and consequently streptomycin alone is the drug of choice for routine use. The principal indication for the streptomycin-dihydrostreptomycin mixture is as a substitute of equal potency for streptomycin in patients in whom severe giddiness or ataxia would otherwise call for a reduction in the dose or the abandonment of antibiotic therapy.

The damaging effect of streptomycin on the vestibular portion of the eighth nerve has had an interesting occasional application in the treatment of certain patients suffering from Ménière's disease, in which the condition is bilateral and the disability is severe. Such therapy should be carried out only by those experienced in the assessment of the finer aspects of vestibular and auditory function.

Sensitivity reactions.—Severe anaphylactoid reactions have been reported

and at least one of them has been fatal after streptomycin (Welch *et al.*, 1953) and also after dihydrostreptomycin (Levi-Valensi and Molina, 1951). Fortunately, the total incidence is much less than that following penicillin, but it is enough to make inquiry regarding sensitivity and allergic disease advisable before starting treatment. Fever sometimes develops ten to twenty-five days after the onset of treatment as a manifestation of sensitivity, and a rise of temperature in these circumstances should be regarded as being due to hypersensitivity until proved otherwise. The drug should be stopped until the fever has subsided and then a test dose of 0.25 g. or 0.5 g. should be given. If streptomycin is not stopped serious damage to the liver or brain may ensue.

Skin eruptions as a result of acquired sensitivity from contact with streptomycin are even more common than in the case of penicillin. The Ministry of Health (1953) carried out an investigation into the incidence of skin reactions among persons handling or administering streptomycin and penicillin. Information was obtained from 70 local health authorities and 76 hospitals for diseases of the chest. The incidence of sensitization in those exposed to the risk was estimated to be 3.5 per cent.: 188 cases were sensitive to streptomycin and 80 to penicillin. This report emphasized that a very early sign of sensitivity to streptomycin was swelling of the eyelids. It is important to avoid the contamination of the hands and face which may readily occur if the syringe is held vertically at eye level and air expelled from it before injection. The exact dose should be drawn directly into the syringe from a rubber-capped vial and the same needle should be used for withdrawal and injection. For streptomycin a No. 14 or even No. 17 needle is recommended. If one person has to give many injections more stringent precautions are advisable, including the wearing of rubber gloves and a mask.

Crofton (1953) points out that patients who acquire hypersensitivity to streptomycin can usually be desensitized, a process which is more difficult but feasible in the case of streptomycin handlers. The technique involves a course of intramuscular injections gradually increasing from 10 μg. to 1 g. over a period of several weeks. It is not yet known how permanent the resultant immunity may be, but even a temporary remission is important to a nurse whose livelihood involves continued contact with streptomycin.

Hypersensitivity in a patient receiving streptomycin can be controlled by the simultaneous administration of corticotrophin (Houghton, 1954). The deleterious effect of this hormone on the progress of tuberculosis does not occur in the presence of adequate anti-tuberculous chemotherapy. Such combined hormonal and antibiotic therapy has a place when hypersensitivity would otherwise demand the withdrawal of streptomycin in a patient who may be in urgent need of the antibiotic. In some cases on withdrawing the hormone the patient is found to have lost his hypersensitivity to streptomycin.

Serious but rare reactions.—Three fatal cases of staphylococcal enteritis have been reported following combined streptomycin and penicillin therapy (Fairlie and Kendall, 1953), and the same authors report two other patients who survived and in whom the clinical picture was identical. The onset of diarrhœa in any patient on any form of chemotherapy must be investigated critically. Blood dyscrasias have rarely been attributed to streptomycin but aplastic anæmia (Deyke and Wallace, 1948; Womack and Reiner, 1951; Sacks *et al.*, 1951) and thrombocytopenic purpura (McDermott, 1947; Rudensky and Fisher, 1951) have been reported.

Other effects.—Reactions from impurities such as histamine and pyrogens are rarely seen with the highly purified preparations which are now in general use. A few trivial but unpleasant symptoms may occur a few hours after an intramuscular injection of streptomycin: notably paræsthesiæ in and around the mouth, vertigo, headache and lassitude. They have been shown to occur less commonly when the patient is at rest, and to coincide with the higher level of streptomycin found in the blood after exercise than when at rest (Riches, 1954). This author showed that the frequency and severity of these symptoms could be decreased by a period of rest after the injection: e.g., by giving the injection in the evening.

Streptomycin and its metabolic products which are excreted in the urine reduce Benedict reagent and, like *para*-aminosalicylic acid and isoniazid, give a false positive reaction for glycosuria some three to eight hours after the intramuscular injection of one gramme.

It may be concluded that, whilst it is salutary to remember that the streptomycins are potentially dangerous, serious reactions to them are exceptional, and that adverse effects such as ototoxicity and hypersensitivity can be reduced to a minimum with careful use of these antibiotics.

DOSAGE AND ADMINISTRATION

Streptomycin may be given orally, intramuscularly or intrathecally. There is very little absorption of the drug from the alimentary canal. The oral dose is 0.5 to 1 g. twice or thrice daily but its use by this route has a very limited application as intestinal organisms readily acquire resistance, even when streptomycin is combined with other chemotherapy.

Streptomycin is rapidly absorbed after intramuscular injection. It appears in the bile and in ascitic fluid but does not appear in effective concentrations in the cerebrospinal fluid. It can be detected in the blood for approximately twelve hours after an intramuscular injection of 0.5 gramme. If kidney function is normal some 60 per cent. of the antibiotic is excreted in the urine within twenty-four hours—mainly in the first four hours. In the presence of kidney disease excretion may be much delayed, with a consequent cumulative increase in the blood level and an increased danger of toxic effects. Streptomycin sulphate is the preparation of choice—it causes less pain on intramuscular injection than streptomycin hydrochloride or the calcium chloride

complex. If 1 g. of streptomycin sulphate is administered intramuscularly as a 2-ml. injection, significantly less delayed pain can be expected compared with its administration as a 4-ml. injection. Viscosity precludes the use of less than 2 ml. (Stradling and Kreeger, 1954).

The usual intramuscular dose of streptomycin is 1 g. daily. This should not be exceeded if administration is to be prolonged. For acute infections 0.5 to 1 g. may be necessary at eight- or six-hourly intervals but doses of the higher order must not be continued for more than four or five days. Dihydrostreptomycin may also be prescribed as the sulphate in doses of 1 g. but its use alone has been abandoned because of its incapacitating toxic effect upon the eighth nerve. Combined with streptomycin it has a limited place, in doses of 0.5 g. each, when symptoms due to vestibular damage are troublesome.

If intrathecal administration of streptomycin is indicated the dose should not exceed 100 mg. of streptomycin sulphate at a single injection. Dihydrostreptomycin should not be given intrathecally as deafness very often results.

It is pertinent again to emphasize here the importance of avoiding contamination of the hands or face when administering the drug if contact dermatitis is to be avoided (Ministry of Health, 1953).

CONDITIONS IN WHICH STREPTOMYCIN IS THE ANTIBIOTIC OF CHOICE

There are three sets of circumstances in which streptomycin is particularly indicated: (1) Tuberculosis. (2) Subacute bacterial endocarditis (in conjunction with penicillin). (3) A miscellaneous group of infections due to gram-negative organisms among which the more important in Great Britain are peritonitis and certain urinary-tract infections.

TUBERCULOSIS

It is generally agreed today that any form of active tuberculosis should receive chemotherapy. Any two of the team of three, streptomycin, isoniazid and *para*-aminosalicylic acid (PAS), may be chosen according to the individual circumstances. Although streptomycin is a powerful weapon in the treatment of tuberculosis it ranks second to isoniazid which is more potent, more effective in tuberculous meningitis and less toxic. The risk of the emergence of resistant organisms is such that no chemotherapeutic agent should ever be employed alone. Valuable information as to the best form of combined therapy has been yielded by the clinical trials carefully planned and conducted by the Medical Research Council in Great Britain and by the Veterans Administration and Public Health Service in the United States. The present status of the chemotherapy of tuberculosis has recently been reviewed in the light of this work by Scadding (1955) and by Crofton (1955). The latter has summarized the position under the apt headings of 'good chemotherapy, risky treatment, bad treatment and salvage treatment'.

'Good chemotherapy' includes 1 g. of streptomycin daily plus 100 mg. of isoniazid twice daily, or 1 g. of streptomycin daily plus 5 g. of PAS four times daily, for patients under 30 years of age. In view of the risk of giddiness, older patients should be given 1 g. of streptomycin twice or thrice weekly plus 100 mg. of isoniazid twice daily plus 5 g. of PAS twice or four times daily. With chemotherapy of this order tubercle bacilli should be cleared from the sputum within six months even in the presence of cavities, and virtually no resistant organisms should emerge. Most patients should have returned to work in twelve to eighteen months. Streptomycin twice weekly with either isoniazid or PAS in full doses daily is regarded as 'risky treatment' in view of the danger of the development of resistance. The use of a single chemotherapuetic agent is 'bad treatment'. 'Salvage treatment' is used when resistance has developed to one or more agents, and consists of a combination of the drug to which the organism is still sensitive, with viomycin, oxytetracycline or pyrazinamide.

The duration of chemotherapy has progressively increased and now it is given continuously for twelve or eighteen months or even longer. Scadding (1955) prescribes antibacterial treatment for at least three months after the last evidence of activity of disease has disappeared and for considerably longer than this in cases in which the disease originally was at all extensive.

Blanco (1954) has graphically illustrated how the mortality from tuberculosis has been halved throughout the civilized world in the five years following the introduction of streptomycin and how a further fall occurred in the year 1952 following the introduction of isoniazid. As another example of the results of modern chemotherapy there may be quoted a series of 107 cases of phthisis of whom 31 had advanced, 48 had moderate and 28 had minimal disease observed over one to three years. Only two died; all the others became sputum-negative and 97 per cent. were fit for work (Crofton, 1955).

In spite of the excellent results the chemotherapy of tuberculosis must not be viewed with complacency. Further clinical trials are still being conducted. Problems continue to be posed by resistant organisms, by the toxic effects of treatment and by inaccessible bacilli. There is much to be learnt about the factors determining host resistance. Other medical and surgical measures have still their part to play and the early diagnosis of disease remains a Public Health problem.

Recently reports have appeared on chemotherapy combined with corticotrophin in the treatment of tuberculosis (Houghton, 1954). By suppressing the inflammatory response to infection and by inhibiting the formation of granulation and fibrous tissue it is possible that tubercle bacilli, otherwise inaccessible, may be exposed to, and destroyed by, chemotherapy. Clearly, further experience of this form of treatment is necessary together with study of the complex issues involved as regards pathology, bacteriology and immunology.

As *sarcoidosis* may be related to tuberculosis, streptomycin has been tried in the former condition, with some success. More striking results have been obtained with cortisone given for short periods, but relapse is common. The next step was to try combined therapy over longer periods and experience with this has been reported by Hoyle *et al.* (1955). These authors conclude that the treatment of pulmonary sarcoidosis is still unsatisfactory. Patients with recent disease and minor symptoms can with safety remain under observation as many improve spontaneously within a year. If there is no improvement, chemotherapy is indicated, followed by cortisone if the situation is unaltered. The combined therapy is continued for at least a year. Some encouraging results have been obtained in suitable cases. Treatment is unlikely to be successful when sarcoidosis is extensive and of long standing with much fibrosis.

SUBACUTE BACTERIAL ENDOCARDITIS

When this infection has been caused by an organism relatively resistant to penicillin, and particularly in the case of enterococcal (e.g. *Strep. fæcalis*) infection, excellent results have been obtained with penicillin and streptomycin given concurrently. This is the best example of the synergistic effect of these two antibiotics. The *in vitro* sensitivity of the organism will determine dosage. About 10 mega units of penicillin daily and 1 to 2 g. of streptomycin daily will be required. The success of penicillin combined with streptomycin in difficult cases of subacute bacterial endocarditis has led to this treatment being employed at the Mayo Clinic in infections due to penicillin-sensitive strains of *Strep. viridans*, and completed successfully in a fortnight (Geraci, 1955). Although the immediate and subsequent results appear satisfactory, further critical evaluation of this scheme is clearly indicated before such short-term therapy is employed as a routine.

CERTAIN INFECTIONS DUE TO GRAM-NEGATIVE ORGANISMS

Peritonitis and enteritis.—In the prevention and treatment of peritonitis the combination of streptomycin and penicillin has proved its value clinically in surgical and gynæcological practice. It is widely and successfully used in the management of perforated abdominal viscera, subphrenic abscess, acute cholecystitis, diverticulitis and pelvic sepsis.

In an attempt to sterilize the bowel prior to surgery of the colon streptomycin has been used orally in doses of 1 to 2 g. daily. Even when one of the poorly absorbed sulphonamides is given at the same time it is probable that many organisms, originally sensitive, rapidly acquire resistance to streptomycin. The patient is therefore deprived of the benefit of this antibiotic should he require it during the postoperative period in the event of the development of peritonitis. This rapidly acquired resistance is probably the reason why oral streptomycin is inferior to the tetracyclines in the treatment of Sonne dysentery (Abbott and Parry, 1955).

Certain urinary-tract infections.—In general, in the treatment of acute infections of the urinary tract, such as pyelonephritis, cystitis and prostatitis, the sulphonamides remain the first choice. If their use does not result in a satisfactory clinical response in a few days the exact nature and sensitivity of the infection should be determined. Many of the chief offenders, e.g. *E. coli*, *Ps. aeruginosa* or *Proteus vulgaris*, are sensitive to streptomycin *in vitro* but treatment with this antibiotic gives variable results mainly because of the development of resistant organisms within forty-eight hours and partly because of neglect to ensure that the reaction of the urine is alkaline. The development of resistance may be delayed by multiple chemotherapy, e.g. streptomycin plus sulphonamide (Klein and Kimmelman, 1947). The base streptomycin is largely inactivated by acid urine, and therefore sodium bicarbonate or sodium or potassium citrate should be prescribed in doses of 2 g. four-hourly, and the urine tested daily with indicator papers to ensure that the pH is near 8. As streptomycin is rapidly excreted in the urine after intramuscular injection, doses of 0.5 g. at six- or eight-hourly intervals are indicated over a period of three or four days. If treatment is successful the urine is sterile in about forty-eight hours. Even smaller doses may be equally effective and may be less liable to promote the development of resistant organisms (Gould *et al.*, 1953).

Miscellaneous infections.—In the treatment of infections due to *H. influenzæ* streptomycin has an important part to play when it is combined with penicillin and in Friedländer's pneumonia when combined with tetracycline. In undulant fever the best treatment is probably the simultaneous administration of streptomycin, tetracycline and sulphonamide. On the basis of ten years' experience of brucellosis in Kenya, and more particularly as the result of a study of 70 consecutive patients from whom the causal organisms were recovered, Wright *et al.* (1953) suggest that chlortetracycline alone may suffice for the early uncomplicated case but that the triple combination is indicated for the chronic or relapsing patient. Oxytetracycline, dihydrostreptomycin and sulphadiazine was the only combination which regularly sterilized the tissues of infected white rats (Jacotot and Vallée, 1954). Authoritative reports of the value of streptomycin in plague and in tularæmia are given respectively by Meyer *et al.* (1952) and by Keefer *et al.* (1946).

CONTRAINDICATIONS

The danger of toxic effects in patients with seriously impaired renal function is such that streptomycin must not be prescribed unless in doses much smaller than is customary. Streptomycin must not be used in a patient hypersensitive to it without the appropriate precautions previously discussed. In the treatment of tuberculosis streptomycin must never be used if there is reason to suspect that the patient is infected with organisms resistant to the antibiotic as a result of previous treatment. Not only would the antibiotic be of no value in these circumstances but whatever other chemotherapeutic

agent was used in conjunction with it would rapidly be rendered useless as the tubercle bacilli acquired resistance. In these circumstances treatment with streptomycin must be postponed until the results of sensitivity tests are known.

CONCLUSIONS

Apart from its major importance in the treatment of tuberculosis, streptomycin has a limited but clearly defined place in medicine and surgery. Its toxic effects can be reduced to a minimum. The main problem is the facility with which bacterial resistance is acquired but in many instances this can be overcome by combined chemotherapy—a practice that is generally undesirable in other circumstances. Streptomycin finds its use, more in hospital than in domiciliary practice, as one important member of a carefully selected team.

I am indebted to many colleagues for the time and patience they have given to discussing the problems involved in the preparation of this article

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CHLORAMPHENICOL

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CHLORAMPHENICOL was one of the earliest 'broad-spectrum' antibiotics to be placed on the market. It was first prepared in 1947 by the fermentation process from *Streptomyces venezuelæ*. In the following year it was synthesized and subsequently the synthetic form and that obtained by fermentation were shown to have the same therapeutic action. The proprietary name of the antibiotic is 'chloromycetin'.

From the practical point of view the most important difference between chloramphenicol and the other broad-spectrum antibiotics is its grave toxic action on the bone marrow. This complication is admittedly rare; nevertheless this does not minimize its seriousness since all elements of the marrow are depressed and the resulting aplastic anæmia is usually fatal. In this article therefore I wish to emphasize the toxicity of chloramphenicol and to make an urgent plea that the drug should be used only in those rare circumstances when other antibiotics are so much less effective that the risk may be considered justifiable. For all practical purposes this confines its use to typhoid fever and possibly influenzal meningitis. The toxic properties of the drug will therefore be described first and its use in infection will then be discussed.

TOXIC EFFECTS

Gastro-intestinal disturbances, including nausea, diarrhœa and vomiting, occur with chloramphenicol as with the other broad-spectrum antibiotics, but their incidence is said to be rather less owing to its rapid absorption. These and other occasional side-effects are relatively unimportant compared with the depressant action of chloramphenicol on the bone marrow.

As early as 1950, Rich *et al.* reported the first fatal case of aplastic anæmia developing in a patient treated for urinary-tract infection. In a survey by the U.S. Food and Drug Administration (Lewis *et al.*, 1952), 139 cases of aplastic anæmia were reported in patients treated with chloramphenicol, 96 of which were fatal. Of these, 44 had received chloramphenicol only and 95 had received the antibiotic together with some other drug. In this country, Hodgkinson (1954) reported the combined results of an investigation by the manufacturers of 'chloromycetin' and an inquiry by the Antibiotics Committee of the Medical Research Council. Over a period of two years, 28 cases of aplastic anæmia and three of granulocytopenia were discovered following the use of chloramphenicol: 24 patients died and at the time of publication three were being maintained by blood transfusion. Only

four patients had recovered, two of these being cases of granulocytopenia.

Certain important facts were brought to light by analysis of this series. Hæmorrhagic manifestations, particularly internal, were the common method of presentation of aplastic anæmia and the first symptom often occurred at an interval which might be as long as two months after the course of chloramphenicol was completed. Adults as well as children were affected. In the majority of cases, this toxic action of chloramphenicol followed heavy and prolonged dosage, often with repeated courses, for such conditions as bronchiectasis, chronic bronchitis and chronic urinary infection. Nevertheless, in some instances, particularly in children, aplastic anæmia appeared after short courses of treatment for acute infections such as whooping-cough and gastroenteritis. In a few instances the total administration was between 6 to 12 g., and the shortest duration of treatment was five days. It was concluded that chronic diseases such as bronchiectasis were unsuitable for treatment with chloramphenicol and that in acute conditions, in which the use of the antibiotic was felt to be justifiable, excessive dosage and prolonged administration should be avoided.

In spite of these reported facts, there is little doubt that chloramphenicol is still widely used, particularly in general practice, in conditions in which other and safer antibiotics would be equally effective. This is borne out by National Health Service figures, which show that in this country about one thousand kilograms of the drug are used annually in hospitals and five to six times this amount in general practice. The joint inquiry described above was a very limited one and from personal communications it is apparent that fatal cases of aplastic anæmia are still occurring after chloramphenicol therapy and are not being reported. Some are undoubtedly missed owing to the time interval which may elapse between the course of treatment and the onset of symptoms of aplastic anæmia. Searching and detailed inquiries of drug treatment should be made in all so-called 'idiopathic' cases of aplastic anæmia or agranulocytosis. It cannot be too strongly emphasized that chloramphenicol is a more dangerous drug than is generally realized and that its use should always be controlled by bacteriological investigation and sensitivity tests.

INDICATIONS

Now that a wide choice of broad-spectrum antibiotics is available it is urgently necessary that chloramphenicol should be limited to the treatment of typhoid fever and influenzal meningitis, as in these conditions it appears to have an action superior to that of any other form of antibacterial therapy at present available.

ENTERIC FEVER

Typhoid fever.—There have been many reports of the use of chloramphenicol in typhoid since the early investigations in which its effectiveness was discovered accidentally during clinical trials in typhus. There is no doubt that with suitable dosage the mortality of the disease is diminished and com-

plications are less frequent. Originally it was thought desirable to start treatment with a large loading dose. This has been abandoned since it may lead to sudden collapse attributed to the release of powerful endotoxins from the typhoid bacilli. A further point is that if inadequate treatment is given, relapses tend to occur more often than in untreated cases. This is probably due to the fact that chloramphenicol is bacteriostatic rather than bactericidal to the typhoid bacillus so that the infection is suppressed rather than eliminated and the development of natural immunity is impaired. Such relapses may be prevented by continuing treatment for a period after the temperature has returned to normal, or by combined antibiotic and vaccine treatment. Even when relapses occur there is apparently no development of resistance to the drug and the therapeutic response is as effective as in the initial attack. A satisfactory dosage scheme in typhoid fever is 50 mg. per kg. body weight daily in divided doses given eight-hourly. This is continued until the temperature becomes normal, after which the dose is reduced to 30 mg. per kg. body weight daily and this is maintained for ten to fourteen days, according to the severity of the case.

Paratyphoid fever is treated similarly and with comparable results. El Ramli (1953) found that rectal administration was useful in infants and young children, or when vomiting was present, or when patients were otherwise unable to cooperate. Chloramphenicol suppositories, 50 mg. per kg. body weight per day, in divided doses gave satisfactory clinical results. El Borolossy (1953) reported effective serum concentrations of the antibiotic with this form of administration.

Typhoid carriers.—Treatment of typhoid carriers with chloramphenicol has proved disappointing, and this again may be partly attributable to the fact that the drug has a bacteriostatic rather than a bactericidal action. Although occasional claims of cure have been made the carrier state has in general experience proved resistant to chloramphenicol, as to all other forms of antibiotic therapy.

INFLUENZAL MENINGITIS

In this serious form of meningitis treatment with antibiotics has completely altered the prognosis. Streptomycin was first found to control the infection but bacillary resistance developed rapidly in some cases. Combined streptomycin and sulphonamide therapy was therefore tried with apparent diminution in failure rate. Apart from the development of resistance, streptomycin has the disadvantage that it must be given intrathecally in order to achieve adequate concentrations in the cerebrospinal fluid. Chloramphenicol, because of its rapid diffusibility, has been successfully employed in the treatment of influenzal meningitis. In the form of 'chloromycetin palmitate' it is easily taken by mouth and, when this is impracticable, it can be given by stomach tube. A loading dose of 75 to 100 mg. per kg. body weight daily is given to start with, followed by 0.75 to 1.5 g. daily for seven to fourteen days according to the severity of the disease and age of the child.

Recent studies of the treatment of influenzal meningitis with chlortetracycline have shown that this antibiotic is also effective, but in severe cases it is probable that the intravenous route should be employed for rapid production of an effective concentration of the drug in the cerebrospinal fluid.

OTHER INFECTIONS

There have been many reports of treatment of acute infections by chloramphenicol, particularly in children; these include whooping-cough, gastro-enteritis, pneumonia and other respiratory-tract infections. There is no doubt that chloramphenicol may be effective in these conditions, but later investigations have shown that chlortetracycline, oxytetracycline or tetracycline is equally effective. When antibiotic therapy is indicated therefore these drugs should be used in preference to chloramphenicol, owing to the possible toxic action of the latter. In recent years, the development of bacterial resistance to antibiotics, particularly of *Staphylococcus pyogenes*, has become a problem of increasing magnitude. It is occasionally found that organisms are still sensitive to chloramphenicol when resistance has developed to penicillin or the tetracycline derivatives. In such instances the organism is almost invariably sensitive also to erythromycin and this antibiotic should be given preference, particularly in staphylococcal pneumonia or enterocolitis.

CONCLUSION

Chloramphenicol is a stable, easily diffusible, broad-spectrum antibiotic with an antibacterial action closely paralleling that of chlortetracycline, oxytetracycline and tetracycline. It has, however, the grave disadvantage that it may produce irreversible and severe damage in the bone marrow and, although the reported cases of this complication are few, the results are serious and usually fatal. It is strongly recommended that its administration should be confined to typhoid fever and influenzal meningitis, since in these conditions its action is superior to that of other antibiotics and effective treatment can be carried out without excessive or prolonged dosage.

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CHLORTETRACYCLINE

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The discovery of streptomycin, in 1944, stimulated interest in antibiotic substances extracted from the soil, and systematic examination of earth samples resulted in the production, in 1948, of chlortetracycline, the first of the so-called broad-spectrum antibiotics. Oxytetracycline followed, in 1950, and two years later tetracycline itself was prepared. Tetracycline is still largely manufactured from chlortetracycline by palladium-catalysed hydrogenation, though a small amount is extracted from an unnamed Texan streptomyces.

The yellow colour of the substance produced by *Streptomyces aureofaciens* gave rise to the designation 'aureomycin', and owing to some muddle over the registering of 'aureomycin' as a trade name, the drug has retained this as its official name until quite recently. It is now known as chlortetracycline in the *U.S. Pharmacopeia*, and the *British Pharmaceutical Codex* is expected shortly to follow suit.

ANTIBACTERIAL SPECTRUM

The scope of activity of chlortetracycline covers the range of penicillin and streptomycin and extends beyond it in the direction of the larger viruses. In general, gram-positive bacteria are affected by lower concentrations of the drug than gram-negative organisms. Table 1 shows the usual results of *in vitro* sensitivity tests on common organisms; these are paralleled closely by *in vivo* studies.

Very sensitive	Moderately sensitive	Relatively resistant
Streptococci	Meningococci	Proteus
Pneumococci	*C. diphtheriæ*	*Ps. aeruginosa*
Gonococci	*E. coli*	*Salm. typhi*
Clostridia	*A. aerogenes*	Some staphylococci
K. pneumoniæ	Most salmonellæ	
Brucellæ	Shigellæ	
H. influenzæ	*B. anthracis*	
H. pertussis	*M. tuberculosis*	
Some staphylococci		

TABLE 1.—Antibacterial spectrum of chlortetracycline.

A perusal of this table shows that the drug is effective against brucellæ which were not notably combated by other antibiotics before chlortetracycline appeared. It also indicates that chlortetracycline has nothing to contribute to the control of proteus infections and is ineffectual against some

staphylococci, a point of some importance when we come to consider the dangers of the drug. In addition to this wide range of antibacterial action, chlortetracycline is effective against spirochætal diseases, such as leptospirosis icterohæmorrhagiæ, and relapsing fever caused by *Borrelia recurrens*. *Treponema pallidum* has been controlled in rabbits, but no extensive trials in the treatment of syphilis in man have been made. The most important extension of activity over that of previous antibiotics is found in rickettsial diseases and those caused by large viruses. Rocky mountain spotted fever, all the varieties of typhus fever, Q fever and rickettsial pox respond to treatment, and the large viruses of the psittacosis group and lymphogranuloma venereum are also controlled. In high concentration the drug destroys amœbæ. Chlortetracycline is without effect on yeasts and fungi and the true viruses. It does not significantly modify the activities of plasmodia.

It must be emphasized that to all intents and purposes the scope of chlortetracycline is identical with that of oxytetracycline and of tetracycline itself. Individual strains of the organisms mentioned may be more sensitive to one member of this group of antibiotics than another, but there is no way of forecasting this from the morphology of the bacterium, and the question has to be decided by sensitivity tests in the laboratory. An organism resistant to one member of the group will not be sensitive to another.

The occasional report of a satisfactory clinical result from treatment by chlortetracycline of a disease caused by an organism said to be resistant *in vitro* can sometimes be accounted for by the fact that chlortetracycline is relatively unstable, and so gives misleading results on laboratory testing. This difficulty may be overcome by careful laboratory control, or by testing sensitivity to oxytetracycline or tetracycline, which are more stable.

Since chlortetracycline is commonly given by mouth, it is important to note here its action on the usual bacterial flora of the intestine. The stools become softer and less odorous, and this is correlated with the suppression of growth of coliforms and gram-positive spore-bearers; these organisms only develop resistance slowly and the gut flora may be kept altered for some months by chronic medication. Yeasts, proteus, pseudomonas and some fæcal streptococci can be shown to increase, but this is of no importance to the patient. The danger of superinfection by *Staph. pyogenes*, however, is very real and will be discussed later.

RESISTANCE

As has been mentioned, resistance of bacteria to the drug develops slowly, but this does not imply that it is not a serious problem, and must not be allowed to encourage indiscriminate use of chlortetracycline. It is significant that over 50 per cent. of all staphylococci encountered in hospital practice in a 1953 survey in the United States were found to be resistant to chlortetracycline (and to oxytetracycline and tetracycline). In this country it is probable that the figure is not so high, as the drug has been less extensively used.

MECHANISM OF ACTION

This is as yet uncertain. It is known that glutamate cannot be incorporated into the bacterial cell protein if chlortetracycline is given, and this raises the question as to whether the drug interferes in some way with this protein synthesis; but there is not yet enough information available to determine its mode of action. The serum levels of the drug attainable by oral dosage are sufficient to inhibit growth, but seldom kill the organisms.

DOSAGE

The determination of dosage naturally depends upon an understanding of the absorption of the drug, its distribution through the body and its excretory routes.

Oral administration gives rise to adequate serum levels in two to four hours and these are maintained for six hours. It follows that a loading dose is unnecessary, and no useful purpose is served by giving the drug more often than once in six hours: 250 mg. repeated six-hourly gives a sustained serum level of 1 to 3 μg. per ml., and this is sufficient to combat most sensitive organisms; 500 mg. repeated six-hourly may raise the serum level to 3 to 5 μg. per ml., and 1000 mg. to more than 5 μg. per ml., but the capacity of the gut to absorb the drug is limited. Large doses are thus not advisable, since little increase in serum level is achieved at the expense of exposing the patient to a risk of toxic effects. The dosage should always be kept as low as is compatible with effective serum levels. Absorption is not interfered with by milk or other food; this is fortunate, since many people become nauseated by the drug, and this may be avoided by giving it with milk. Most antacids allow of its normal absorption, but aluminium salts and silicates may interfere with it and must be avoided.

Chlortetracycline is not well absorbed if given intramuscularly, but intravenous administration of 250 mg. readily gives a serum concentration of 5 to 10 μg. per ml., and there may still be 1 to 2 μg. per ml. present twelve hours after a single dose. There are practical difficulties in intravenous administration which derive from the irritant nature of the drug. It must be diluted in isotonic saline or dextrose solution to a concentration of not more than 5 mg. per ml. Infections demanding the intravenous route usually need a daily dose of 1 g. This may be given in two injections of 500 mg. in at least 100 ml. and must be administered at a slower rate than 2 ml. per minute if venous thrombosis is to be avoided. This is a tedious procedure, and in practice the drug is usually given into a continuous intravenous drip.

Chlortetracycline reaches a high concentration in kidney, spleen, liver and lung, but is concentrated highest in bile, where levels ten times those in serum may be encountered. Concentrations in pleural fluid and ascites are lower than those in serum. Cerebrospinal fluid concentrations are also lower and are unaffected by the presence of meningeal inflammation. The drug passes through the placenta and gives rise to a fœtal concentration about half that of the maternal blood.

It is slowly excreted by the kidneys, and up to 50 per cent. of an oral dose can be recovered from the urine in three days. Fæcal excretion accounts for another 10 per cent. The means by which the body disposes of the balance of 40 per cent. is unknown.

CONDITIONS IN WHICH CHLORTETRACYCLINE IS THE ANTIBIOTIC OF CHOICE

The chief advantages shown by chlortetracycline over its predecessors were the efficacy of treatment by mouth, coupled with low toxicity and a wide range of action. These qualities are shared by the other members of the group, oxytetracycline and tetracycline, and it is almost true to say that an indication for one member of the group is an indication for any member of the group. There is certainly no profit in considering their application separately although, as has already been remarked, individual strains of bacteria may be encountered which are more sensitive to one member of the group than the others; this cannot be forecast and must be assessed by laboratory tests.

Chlortetracycline should be used in the treatment of two groups of disease:—

(1) Those in which the causal organism is usually sensitive to the antibiotic and not to other less toxic drugs such as penicillin and the sulphonamides.

(2) Those caused by bacteria usually responsive to penicillin or sulphonamides, but which have become resistant to these drugs.

In the first group we must note brucellosis. A course of 2 g. daily for ten days should control the fever and symptoms. Relapses may occur but do not seem to be due to resistance of the brucella and are controlled by a second course of treatment. Psittacosis and other virus infections of the psittacosis group respond well to chlortetracycline (2 g. a day for seven days), but the effect of the drug is less predictable in other virus ('atypical') pneumonias, and is not indicated as a routine treatment, although it may be given if the patient is very ill. Lymphogranuloma venereum is well controlled, elementary bodies disappearing from the buboes which become smaller in about a week; this condition needs more prolonged treatment, however, and the drug should not be withdrawn for at least four weeks. There is a case to be made out for its use in multiple venereal infections, but it must be remembered that it may mask the presence of syphilis.

In the second group, the drug is useful in any severe staphylococcal infection which resists penicillin, in any salmonella or shigella infection which is not controlled by sulphonamides, and in some urinary infections which have not responded to ordinary treatment. In the control of urinary infections, however, its use is limited by its need of an acid medium for effective action; this cannot be achieved if the offending organism is a proteus or *Ps. aeruginosa*.

It may be used in ocular conditions caused by appropriate organisms, and

is effective in acute, but not chronic, trachoma. Its effect in amœbiasis has been disappointing: the acute intestinal symptoms are controlled, but the relapse rate is unaffected and it does not modify the course of hepatic amœbiasis. Its capacity for altering the bacterial flora of the gut has led to its use in the treatment of hepatic coma, in the hope of reducing ammonia formation in the bowel.

CONTRAINDICATIONS

The continued emergence of resistant strains of bacteria places a serious responsibility on the doctor who prescribes chlortetracycline. It should be reserved for the conditions outlined above, and it should not be used for minor staphylococcal infections, virus diseases other than the psittacosis group, or chronic respiratory conditions. The response of enteric fever is poor, and both this and influenzal meningitis are better controlled by chloramphenicol, whilst meningococcal meningitis is best treated by a sulphonamide.

The presence of renal or hepatic disease need not be regarded as a contra-indication to the use of the drug. Although very large intravenous doses have been reported to cause liver damage, this observation has little bearing on the clinical problem. Indeed, there is a suggestion that chlortetracycline in normal dosage may be beneficial in acute viral hepatitis, but its action in this respect is not sufficiently certain to recommend its routine use.

Chlortetracycline should only be given concurrently with penicillin after careful thought. Although penicillin does not impair the efficacy of the drug, chlortetracycline is often antagonistic to the action of penicillin.

TOXIC EFFECTS

The most common toxic effects result from the irritant action of the drug on the alimentary tract. Nausea, vomiting, epigastric discomfort and diarrhœa are familiar symptoms to anyone who has used chlortetracycline. As happens so often with a new antibiotic, however, the quantity initially prescribed is usually excessive, and the toxic effects are encountered less often as experience determines the minimal effective dosage. With chlortetracycline it is unusual to find toxic symptoms on daily dosage of less than 1.5 g., and the gastric disturbances can be limited by giving milk with the drug. These symptoms do not occur with parenteral administration.

Various unpleasant phenomena may occur in the mucosa at the two ends of the alimentary tract and in the perineum. Angular stomatitis, glossitis, xerostomia, sore throat and dysphagia vie with pruritus ani and anal fissure, scrotal itch or vulvo-vaginitis in contributing to the patient's discomfort. It is known that chlortetracycline alters the bacterial flora of the gut, and that bacteria add to their host's well-being by helping with the synthesis of vitamins. These toxic effects may be partly relieved by giving vitamin B complex, but withdrawal of chlortetracycline is nearly always necessary if the mucosa is to return to normal. These symptoms are annoying but not

serious. It is a different matter, however, if the alteration in bacterial flora allows another organism to get a hold on any part of the alimentary tract; this happens much less commonly, and results in either moniliasis or superinfection with *Staph. pyogenes*.

Moniliasis is usually confined to the mouth which becomes very sore, interfering with eating and may thus make inroads into the patient's reserves which he can ill afford. Sometimes the infection is only around the anus, where the skin becomes extremely itchy, and this pruritus often deprives the patient of sleep. Rarely, the characteristic membrane extends from the mouth down the upper respiratory tract, and some observers believe that a true monilial pneumonia occurs, although it is difficult to be sure that the lung has not been consolidated in consequence of aspiration. If this happens it often takes a matter of months to clear up. In the face of any monilial infection chlortetracycline must be stopped at once, other antibiotics be avoided, and attempts made to control the fungus by gentian violet. Claims have been made that the incidence of monilial complications may be reduced by giving undecylenic acid orally at the same time as chlortetracycline.

Moniliasis does not prove fatal, but death may occur from bacterial *superinfection* of the gut. This is heralded by diarrhœa and is sometimes precipitated by a purgative. A return of fever, the increasing illness of the patient and the presence of pus in the stools indicate that this is no ordinary diarrhœa and that a staphylococcal enterocolitis is present. It is imperative to stop chlortetracycline at once if the patient's life is to be saved. Erythromycin, 200 mg. four-hourly by mouth, should be given in the hope that the superinfecting organism is sensitive to it.

Among the less common and less important toxic manifestations that have been recorded are drug fever and various skin rashes. Dizziness and vertigo have been observed but are rare. The local irritant effect of the drug has already been mentioned in connexion with intravenous administration. This disallows its use in the pleural cavity and renders intramuscular injection painful.

CONCLUSION

The discovery of chlortetracycline has extended the range of infective illnesses which may be brought under antibiotic control, and the drug has earned a firmly established place in clinical practice. Its actions are paralleled by those of oxytetracycline and tetracycline, and these three members of the group can hardly be considered apart from one another.

Minor gastro-intestinal toxic effects can be reduced by limiting total dosage, but oral and anal moniliasis remain troublesome, and purulent enterocolitis may still prove fatal.

OXYTETRACYCLINE

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Oxytetracycline, chlortetracycline and tetracycline are three analogues which have an almost complete similarity: (a) in the wide range of their antibacterial activity; (b) in the capacity to produce resistant strains of micro-organisms which have the characteristic that the acquired resistance is common to all three; (c) in the pattern of side-effects which they may produce. Further, for each of them it might be said that in their strength lies their weakness; for the broad spectrum of their activity means that their antibacterial effect is indiscriminate against friend and foe. Although this should never inhibit the physician from prescribing them when indications arise which suggest their possible usefulness, it should make him cautious in their administration and encourage their avoidance when another remedy will be just as effective. As a generalization it may be said that only too often antibiotic therapy is prescribed unnecessarily for illnesses in which the natural recovery rate is high; we need reminding that these undoubtedly potent remedies (of which oxytetracycline is an example) can induce changes in the patient which may not only be disturbing but indeed prove fatal.

The chemotherapeutic spectrum of oxytetracycline is wide. It has been shown to be effective against the common gram-positive organisms—pneumococcus, streptococcus and staphylococcus—and against many important gram-negative organisms, such as *E. coli*, salmonella, shigella, meningococcus and gonococcus. Perhaps of greater importance has been the discovery of its effectiveness against two groups of infections due to micro-organisms which are at least near-virus in character, namely, the rickettsial and the psittacosis-lymphogranuloma infections. The extracellular position of the pathogen in most bacterial infections makes it easily accessible to antibacterial agents. The intracellular position of the parasite in virus infections made it seem unlikely that an agent could be produced which could destroy the virus without at the same time damaging vitally the cell upon which it depended for its metabolic activities. The inclusion of rickettsia and psittacosis in the list of successfully chemically treated infections is therefore an important advance. But this at present marks the limit of progress. There have been claims for the efficacy of oxytetracycline in such virus diseases as mumps, infectious mononucleosis, chickenpox and herpes zoster, but such claims are outweighed by reports of controlled experiments which have shown a complete lack of response. There is therefore no justification for using oxytetracycline in virus infections uncomplicated by secondary bacterial invasion.

DOSAGE

When first introduced a daily dosage for adults of 3 to 4 g. was suggested,

treatment being often started with a 'loading' dose of 1 to 2 g. Experience has shown that this daily dose is too high and that a large initial dose is unnecessary. There is more than a suspicion that the incidence of side-effects is increased when large doses are used. As a general rule therefore the maximum daily dose for adults is 1.5 to 2 g. This is still often given divided into four-hourly or six-hourly amounts but it is probable that twelve-hourly administration is just as effective. It seems possible that some of the gastro-intestinal upset is due to direct toxic action in the bowel and for this reason no single dose should exceed 1 g. Administration with milk is convenient—especially in children—and may reduce toxicity. The use of lactobacillary preparations (milk or cheese) has been tested but so far the results are inconclusive.

UNWANTED SIDE-EFFECTS

The microflora of the mouth and bowel is not upset with impunity. Oxytetracycline effects a considerable change in the bacterial flora of these sites which, at least in part, may be responsible for the frequency with which its use is associated with disturbing gastro-intestinal symptoms. In this respect oxytetracycline is more upsetting than its near-relatives, chlortetracycline and tetracycline. This would support the view that local irritation plays a role in inducing side-effects. It has been suggested that some of the symptoms arise from vitamin deficiencies induced by the drugs and there is no doubt that animal experiments have been reported in support of this contention. These experiments, however, are somewhat artificial and bear little resemblance to the conditions of normal therapy. For most acute infections the period of therapy should not exceed four to five days and it is hard to believe that a severe degree of hypovitaminosis could develop in this time. In my own experience vitamin complexes have not prevented the appearance of all varieties of side-effects. Their routine use is not recommended.

Moniliasis.—The main effect upon the microflora which can be shown to accompany oxytetracycline therapy is overgrowth of *C. albicans* and *Staph. aureus*. The former (which can, of course, normally be isolated from a proportion of patients if appropriate examinations are made) will be found in heavy growth in the sputum and fæces of about two-thirds of those undergoing oxytetracycline therapy. This statement may well exaggerate the danger for, in my own experience, it has not proved possible to incriminate this overgrowth as a cause of any of the usual side-effects. Nevertheless, there is some evidence that oxytetracycline acts not only as a growth stimulant of *C. albicans* but may enhance its pathogenicity. Such changes are potentially dangerous in the elderly, in those with established chronic pulmonary disease and in the infant.

Superinfection with staphylococcus has proved rather more important. The main site of this superinfection is the bowel but it has been observed in the throat, the sputum and the urine. The staphylococci are resistant to oxytetracycline. *Staph. aureus* is normally present in the fæces of a pro-

portion of persons; during oxytetracycline therapy, however, a moderate to heavy growth may be observed in upwards of 90 per cent. of patients. In a hospital ward, where many of the patients are receiving the antibiotic, this has given rise on occasions to outbreaks of staphylococcal infection, the most serious aspect of which is the occasional occurrence of a profuse cholera-like diarrhœa from which a pure culture of staphylococci can be obtained. Some of these cases have died, partly from the overwhelming dehydration, but probably also in part due to absorption of toxic substances from the bowel. It must be said at once that such a condition may well be more of a danger in a hospital ward where continuous cross-infection from patient to patient is constantly occurring than in general practice where each patient is treated more or less in isolation. None the less it is a side-effect, the importance of which cannot be overemphasized. Not the least dangerous aspects of the complication are the suddenness with which the diarrhœa appears and the rapidity of the deterioration of the patient.

Gastro-intestinal disturbances.—From the clinical point of view the most common complaints during treatment are epigastric distress, nausea, vomiting or diarrhœa, and one or other or a combination of these may be expected in about a quarter of those treated. It is unusual for the complaint to be so severe that the patient refuses to take the antibiotic. The stools become more bulky even when actual diarrhœa is not mentioned, but in about half of the patients comment may be expected that the consistence of the stool is softer than normal and that more than one stool is passed in the day. A few patients complain bitterly of a severe burning pain on defæcation. The tongue often acquires a glossy atrophic appearance and actual glossitis and stomatitis occasionally occur. The most striking abnormality of the mouth is the appearance of a 'black tongue' which, in one series of my cases, was observed in 5 per cent. of those treated. A particularly distressing complaint—especially in the female—is of extreme soreness and severe pruritus around the perineum which can persist for weeks after treatment has stopped.

Such complications are encountered with all of the tetracyclines. As has already been said, there is an impression that they occur more often with oxytetracycline than with tetracycline itself, but this may merely be a reflection of the fact that experience of the latter is of shorter duration.

Sensitization.—Mention must also be made of the complication—increasing in its frequency—which is common to all chemotherapeutic agents, namely, sensitization. With oxytetracycline we may expect to see a greater proportion of cases as its use increases. The important aspect to be emphasized is the need to keep treatment of as short duration as possible—four to six days at the maximum. Local skin sensitization from the use of salves or ointments containing oxytetracycline is already occurring. For this reason topical application must always be questioned. This form of sensitization is usually a consequence of prolonged use—sometimes indeed as a result of self-medication with the remainder of an ointment previously

prescribed. The destruction by the doctor of ointments containing antibiotics after the course of therapy is completed should be seriously considered.

INDICATIONS

It may seem somewhat unusual—perhaps, indeed, unfair—to precede a discussion of the therapeutic indications for oxytetracycline by a section on its untoward reactions. But such a presentation has been purposive—the intention being to draw attention to the almost unpredictable nature of the changes which may accompany the therapeutic interference with the host-parasite complex by using a potent remedy of this character. One may indeed suggest that in routine clinical practice in Great Britain there are few occasions when oxytetracycline should be the antibiotic of first choice. For most of the common infections other forms of chemotherapy are available which are just as effective and freer from side-effects. That the best antibiotic is that most recently discovered and with the broadest spectrum of activity is a dangerous heresy.

Rickettsial infections (which may be encountered in this country mainly in the form of Q fever) and psittacosis constitute absolute indications for one of the tetracyclines.

In regard to other important applications, one must mention first of all the treatment of infections caused by penicillin-resistant staphylococci. In hospitals where penicillin is used routinely it may be assumed that staphylococcal infections acquired in hospital will be penicillin-resistant and some other antibiotic should be used pending reports on the precise sensitivity of the organism. If, of course, oxytetracycline is also being used frequently this antibiotic may likewise prove ineffective. This is one good reason for using the broad-spectrum antibiotics sparingly. The increasing frequency with which organisms are isolated with a varying pattern of resistance also emphasizes the importance of obtaining adequate specimens for bacteriological examination before starting treatment. Although common sense dictates that the physician will often need to begin treatment on the strength of a correct clinical diagnosis and before any assistance can be offered by the bacteriologist, this should not absolve him of the responsibility, in cases in which a precise bacteriological diagnosis can be made, of submitting the necessary specimen.

Pneumonia is now often regarded as a diagnosis which suggests the need for an antibiotic such as oxytetracycline although there are really no grounds for such an assumption. Penicillin proves adequate for 95 per cent. of cases; and a mixture of penicillin and streptomycin—particularly useful in infancy, when a staphylococcal infection may be feared—will prove adequate for almost all cases. That vague clinical entity 'primary atypical pneumonia' is regarded as a condition which may respond to oxytetracycline although the evidence is very conflicting. Two points should be borne in mind. In the first place, all of the available evidence suggests that this condition is uncommon, if not indeed rare, in British practice. Secondly, it is still a

diagnosis which lacks etiological specificity; the clinical picture may be produced by viruses, by rickettsiæ, sometimes by bacterial pathogens and, one suspects, by a bizarre host reaction of a non-infective character. It seems possible that the good results reported by some are explained by the specific etiology of a group of cases or to the presence of a secondary bacterial invader susceptible to oxytetracycline.

Pertussis is an example of a respiratory infection which is responsive only to certain antibiotics, and in view of the severity of the illness in infancy oxytetracycline therapy should always be considered. Chemotherapy of pertussis is only of proven efficacy when it is begun in the early stages of the disease, and is less effective after the second or third week. Treatment should extend for a period of seven days.

Bacillary dysentery is a condition in which bacteriological cure may be achieved more rapidly with oxytetracycline. In my experience this has been done with very low dosage—10 mg. per kg. per day—and, although the antibiotic is not to be regarded as a routine treatment for all cases, it may be indicated in special circumstances; for example, in the treatment of a food handler. By contrast with dysentery the salmonella food-poisoning infections have proved completely resistant.

Two conditions may be mentioned in which oxytetracycline can play a useful part, but in which bacteriological examination must always be carried out before starting treatment with it. In the first place, certain urinary infections respond well. It will usually be found that the simple acute infection due to *E. coli* in the child or young adult clears rapidly with sulphonamides and streptomycin. In the older person, however, there is often some complicating pathology: the infection may be mixed and unusual bacteria may be encountered. Treatment of such cases should not be embarked upon until a complete bacteriological examination has been made. Study of the sensitivity pattern of the organisms may suggest oxytetracycline as the best treatment. The second condition is chronic broncho-pulmonary infection. Here careful bacteriological examination of a specially taken specimen of sputum will include a study of the flora and the sensitivity of the different organisms to antibiotics. Although antibiotic treatment is not to be regarded as a panacea for these cases, there is no doubt of its value in some individuals, and, depending upon the bacteriological report, oxytetracycline can be the drug of choice.

CONCLUSION

It is impossible in the space of a short review to do more than pick out a few of the practical uses of a remedy of such potency. With the increasing number and range of activity of chemotherapeutic substances the choice of antibiotics becomes more and more complex and the practitioner must exercise shrewd judgment in making his choice. He will find that his important ally is the bacteriologist and to attempt the management of severe infections without invoking his aid is quite unrealist.

TETRACYCLINE

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At a recent international symposium it was stated that in the last twelve years some 3,500 different antibiotic substances of varying potency and toxicity have been isolated and studied. This number is steadily increasing and imagination boggles at the future; one is irresistibly reminded of De Morgan's

> 'Great fleas have little fleas upon their backs to bite 'em,
> And little fleas have lesser fleas, and so *ad infinitum*,
> And the great fleas themselves, in turn, have greater fleas to go on;
> While these again have greater still, and greater still, and so on'.

The situation should be a most reassuring one; yet it is far from being so. The first of these drugs to be generally used, penicillin, was so safe that there is not as yet general appreciation of the fact that its successors may be dangerous unless used with extreme care. It is a matter for concern that in the United States some 40 per cent. of prescriptions are for antibiotics, and there can be little doubt that the Continental figures are of a similar order. It looks as though the doctor, instead of being an acceptable friend of an amiable Mother Nature, may become a sort of teddy-boy with an antibiotic cosh confronting a reeling and resentful wraith.

GENERAL CONSIDERATIONS

The year 1947 saw the introduction of chloramphenicol. This was the first of the broad-spectrum antibiotics, so-called because it was active not only against gram-positive and gram-negative organisms but also against rickettsiæ and some large viruses. It is of interest to note that its mirror-image, although identical in chemical structure, possesses practically no antibacterial properties: an example of the fact that activity is dependent upon both chemical and physical features and that closely related compounds can differ materially in biological activity. The tetracycline compounds, chlortetracycline, oxytetracycline and tetracycline, followed, each possessing a wide though not identical field of use.

Chemically, tetracycline differs little from its sister-compounds: from chlortetracycline by a single chlorine atom at carbon 7, and from oxytetracycline by an OH group at carbon 5. It possesses certain advantages over the others, in particular that it is more stable, less likely to produce toxic effects, and achieves a higher blood level with the same dose. Furthermore, it penetrates the cerebrospinal fluid to a much greater extent, particularly in the presence of meningeal irritation. It is readily absorbed from the gastro-intestinal tract and blood stream, and adequate concentrations appear in

the urine, stools, bile, saliva, exudates and transudates, milk, and across the placental barrier. It is bacteriostatic, but in high concentration may be bactericidal. In common with other antibiotics, it has growth-promoting properties in animals, and has been used in veterinary work for nutrition, prophylaxis and treatment. It may also play a part as a crop spray and a food preservative.

CLINICAL ASPECTS

Clinical experience is still to some extent limited and hence the clinicians' findings ('dogmatic statements') may clash with those of the bacteriologists ('science fiction'). It may be recalled that although the typhoid bacillus *in vitro* is sensitive to streptomycin, tetracycline and chloramphenicol, the last is the effective drug in enteric fever. It is of the utmost importance that laboratory aid be sought whenever practicable, to ensure that the infecting organism is a susceptible one and to prevent the development of resistant strains. When a single infecting organism is present, as in typhus or gonorrhœa, treatment is relatively simple; but in infections of, for instance, the genito-urinary or respiratory systems, when there is no constant bacterial cause, treatment without bacteriological assessment is empirical. Bacterial resistance is increasing, and sensitivity tests are rapidly becoming essential even in the mild infections.

The inhibitory concentration of tetracycline in the serum which is achieved with therapeutic doses is about 1 μg. per ml. and at this level the drug is active against a large number of agents: the staphylococcus, streptococcus, pneumococcus, gonococcus, meningococcus, escherichia, salmonella, shigella, brucella, rickettsiæ and amœbæ. In the gram-positive range, it is slightly less effective than chlortetracycline against the streptococcus and pneumococcus but its equal or superior against the staphylococcus. It is, however, the most active of the three tetracyclines in the gram-negative range, except with proteus and pseudomonas.

It is the drug of choice in typhus, undulant fever and bacillary dysentery. Subject to the organisms being susceptible, excellent results can be expected in staphylococcal infections, including skin infections and osteomyelitis (assuming that surgical treatment will be advocated when necessary); in streptococcal infection, including scarlet fever and otitis media; in meningitis, particularly meningococcal and influenzal; in pneumonia, excluding the primary atypical form, and in acute bronchitis; in urinary infections (preferably in the presence of an acid urine) not associated with anatomical aberrations; in alimentary infections: dysentery; in venereal diseases: gonorrhœa, chancroid, lymphogranuloma venereum; in rickettsiæ and virus disease, including psittacosis. It is also of some value in whooping-cough and amœbiasis, but is ineffective in tuberculosis. (*See* table 1.)

Tetracycline may be used in *prophylaxis:* for instance in the surgery of trauma, infected wounds, the colon and lung. It may also be given to patients with rheumatic heart disease prior to dental extraction: in such circumstances it should be given shortly before the operation is undertaken.

Because of the risk of producing resistant bacterial strains and the possibility of converting a simple into a dangerous illness, it is not justifiable to use the drug in mild infections, which are often self-limiting and respond to simple measures, and it is not required in normal labour or in clean

Most Valuable	Valuable	Avoid Use
Pneumococcus, streptococcus, staphylococcus, meningococcus, gonococcus, most gram-negative organisms, brucellosis	*E. coli*, enterococcus, anthrax, influenza	Mild infections
Alimentary infections, bacillary dysentery, peritonitis	Alimentary infection; salmonella, shigella, *E. coli*	Enteric fever
Upper respiratory tract infections, otitis media, pneumonia	Whooping-cough	'Clinical pneumonia', chronic chest infections
Meningitis		
Psittacosis group		Virus infections
Urinary-tract infection without anatomical abnormality		Urinary proteus infection
Gonorrhœa, lymphogranuloma venereum, chancroid	Syphilis	
Typhus, rickettsiæ	Actinomycosis, amœbiasis	Tuberculosis

TABLE 1.—Short list of conditions and organisms responsive to tetracycline. It is assumed that other drugs may have been tried first, that sensitivity of the organism has been ascertained, and that a combination of drugs may be used. (Penicillin and tetracycline should not be used together.) Ancillary measures such as correction of electrolyte balance may be required.

operations. Factors which militate against successful treatment include the severity of the infection, the presence of insensitive or resistant organisms, recurrence of infection when antibiotic therapy is stopped, the development of toxic effects, and defects in the host, such as advanced age, failure of immune response, poor nutrition and debility, or anatomical abnormalities.

DOSAGE

Tetracycline is available in various forms for oral, intramuscular and intravenous use. A simple working rule for assessing dosage is to allow approximately 100 mg. per stone (16 mg. per kg.) body weight daily. The usual preparation is the capsule containing 50 mg. or 250 mg., given by mouth, but if there is overwhelming toxæmia or vomiting, intravenous administration is best. The intravenous preparation is a 1 per cent. solution, each 10 ml. of which contain 10 mg. The average course is made up of a 'loading' dose of 1 g., followed by 250 mg. 6-hourly. Dosage can be increased up to 2 g. a day but this should not be exceeded as at this level the drug is hepatotoxic and an excessive amount passes through the bowel. It is an advantage if the drug is taken during a meal or with a glass of cold milk. If a satisfactory response is not obtained within a few days the diagnosis

should be reviewed and the possible development of resistance or of complications be examined.

If combined therapy is indicated, e.g. when several organisms are present, the added drug should belong to the bacteriostatic group (chloramphenicol, erythromycin) and not to the bactericidal group (penicillin, streptomycin, bacitracin, neomycin) in order that a synergistic effect may be obtained. There is some evidence to suggest that the action of tetracycline may be potentiated by sulphonamides, and that the addition of vitamins is desirable. One commercial preparation contains an additional antibiotic, nystatin (mycostatin), in an attempt to prevent the development of moniliasis.

Resistant organisms usually exhibit cross-resistance to oxytetracycline, chlortetracycline and tetracycline, but this is not invariable and one drug may be effective when another has failed.

TOXIC EFFECTS

It is certain that the Victorian divines would have seized eagerly upon the fact that this beneficent and powerful drug, with its infinite capacity for restoring health and happiness, should yet bear with it the seeds of disharmony, corruption and death. Discretion is called for in its use if it is not to join the high proportion (95 per cent. according to one observer) of misused antibiotics.

Pruritus ani and mouth infections.—These are always associated with fungus infection. Their significance should not be underrated, as with mouth infections there is definite risk of spread to involve either the œsophagus and stomach, or the lungs. The possibility of superinfection increases the potential dangers. Gentian violet, 1 per cent. aqueous solution, is of value in treating the anal lesions. The usual measures of oral hygiene should be adopted from the start, and local treatment may be supplemented by gentian violet, hydrocortisone, or cyanocobalamin, in a strength of 50 μg. per ml., applied two-hourly.

Nausea and vomiting are not uncommon and may be due to a direct action on the stomach. They can be minimized by giving the drug with food or milk.

Superinfection.—Nausea and vomiting may precede the development of superinfection which can be a most dangerous condition. It occurs when the antibiotic alters the flora of the bowel and consequent infection by resistant staphylococci and fungus takes place.

Diarrhœa.—Superinfection is associated with diarrhœa which is itself the most common complication, although it is said to be less often encountered with tetracycline than with the other compounds. It is not *per se* indicative of superinfection, but with superinfection all degrees of illness varying from a mild upset to a dangerous or even fatal enterocolitis may present. Nausea and vomiting may be absent. Should a staphylococcal infection be implicated, the problem of resistance or crossresistance must be investigated and appropriate antibiotics or combinations of antibiotics

be used, e.g. streptomycin with a sulphonamide. A powder, which can be given at frequent intervals in addition to the common remedies, contains bismuth salicylate, 20 grains (1.3 g.), with prepared ipecacuanha, 6 grains (0.4 g.). When the condition is other than of mild degree the patient should be transferred to hospital, as sudden and alarming electrolyte disturbance may take place.

Thrush infection.—This is usually due to the yeast *Candida albicans*, but other fungi may be involved. Moniliasis is difficult to deal with, since little antigen response is evoked and hypersensitivity or toxæmia may develop. The use of iodides is time-hallowed and more recent agents which may help are paralens (methyl and propyl esters of parahydroxybenzoic acid), and undecylenic acid, given orally. Stilbamidine may also be tried. The use of fungicidal antibiotics, such as candicidin, nystatin (mycostatin) and coliformin, is being investigated and it is to be hoped that these will prove of value.

Skin reactions are not common but if they occur are of the allergic type and respond to antihistamine therapy.

Liver damage.—This may occur if the drug is used in high dosage, i.e. exceeding 2 g. daily. It is unlikely to occur in ordinary circumstances, but calls for care when intravenous therapy is being given, because of the high blood concentration achieved.

Failure of immune mechanism.—Tetracycline, like other broad-spectrum antibiotics, appears to act directly and not by enhancing the natural defences of the host; yet such immune mechanisms, evolved over centuries, are of paramount importance and must be preserved. Almroth Wright stressed this long before the antibiotic era, and its importance is again being realized. Artificial agents, including protein shock or vaccines, may prove helpful and the use of pyrogens has recently been mooted.

L'ENVOI

Tetracycline is one of the most powerful and valuable drugs that have become available to medicine. In common with most antibiotics, however, it is a good servant but a bad mistress. It should only be used if simpler measures are unlikely to be successful or when there is a specific indication. The suggestion of the Medical Research Council that such drugs should be reserved for severe infections or organisms insensitive to sulphonamides or penicillin has a great deal to commend it. We have learned much about new drugs in the last ten years but, as Sophocles says, 'Ἔννους τὰ καινὰ τοις πάλαι τεκμάυρεται', a dictum elegantly transformed by Sir Robert Hutchison, in his modern litany: 'From inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, science before art, and cleverness before common sense, from treating patients as cases, and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us'.

ERYTHROMYCIN

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THE antibiotic, erythromycin, is produced during the growth of *Streptomyces erythreus* and was first isolated from samples of soil taken from Panay in the Philippines. Its discovery, reported by McGuire and his colleagues in 1952, came at a time when the magnitude of the problem of bacterial resistance to penicillin and the broad-spectrum antibiotics was being generally realized and it was hailed as a possible answer to the drug-resistant *Staphylococcus aureus*, whose ghost was beginning to haunt the wards and casualty departments of the great city hospitals. Although time has dimmed these early hopes to some extent, erythromycin remains an excellent antibiotic and, if properly used, should continue to be a valuable, if perhaps rather specialized, weapon in our therapeutic armoury.

Erythromycin is predominantly bacteriostatic in action, and in this respect differs from penicillin which has a rather similar antibacterial spectrum. It diffuses freely into the body fluids with the exception of the cerebrospinal fluid, where concentrations are unpredictable and often low. It is excreted in the bile, urine and fæces. It appears to be remarkably non-toxic and can be given easily and efficiently by mouth. In many ways therefore it is an ideal antibiotic, but the comparative ease with which organisms, and especially *Staph. aureus*, develop resistance to it, makes it wise to reserve its use for the special situations to be discussed later.

ANTIBACTERIAL SPECTRUM

Many workers have published the results of testing various strains of bacteria against different concentrations of erythromycin *in vitro*. For further reference, the reader is referred to the work of Haight and Finland (1952), Heilman *et al.* (1952), Herrell (1954) and Powell *et al.* (1953). In general, it may be stated that to be 'fully sensitive', growth should be inhibited by less than 1 microgram per ml., for this concentration can easily be obtained in the blood with normal dosage of the antibiotic. With full and sustained dosage, however, the growth of organisms sensitive to between 1 and 4 μg. per ml. can often be arrested, and these are included as being 'relatively sensitive'. If still higher concentrations are required, bacterial growth is unlikely to be affected and the organism is classed as 'resistant'.

In table 1 the common bacteria encountered in medical practice are subdivided into three classes according to whether they are fully sensitive, relatively sensitive or resistant. It must be remembered that organisms classed as sensitive may become resistant after contact with the antibiotic, and, unfortunately, this is nowhere more apparent than in the case of *Staph. aureus*.

Tunevall and Hedenius (1954) believe that erythromycin exerts an inhibitory effect upon some of the organisms classified as resistant (especially *E. coli*, *Proteus vulgaris* and *Ps. aeruginosa*), and that this explains the observed fact that overgrowth with a resistant organism is less likely to occur after erythromycin therapy than following penicillin.

Fully sensitive	Relatively sensitive	Resistant
Hæmolytic streptococcus	†*Strep. fæcalis*	*E. coli*
Staph. aureus	†*Staph. albus*	*Proteus vulgaris*
Pneumococcus	‡*H. influenzæ*	*Ps. aeruginosa*
N. gonorrhœæ		Salmonella group
*N. meningitidis**		*Shigella flexneri*
C. diphtheriæ		*K. pneumoniæ*
Cl. tetani		*Brucella abortus*
Cl. septicum		
*H. pertussis**		
Brucella suis		
Brucella melitensis		

TABLE 1.—Antibacterial spectrum of erythromycin.

* = Some strains only moderately sensitive.
† = Some strains fully sensitive.
‡ = Strains very variable. Some fully sensitive, others resistant.

Some of the larger viruses, including those responsible for meningo-pneumonitis, lymphogranuloma venereum, and epidemic typhus, are at any rate partially sensitive to erythromycin, as they are to the broad-spectrum antibiotics, chloramphenicol, chlortetracycline, oxytetracycline and tetracycline.

DOSE AND PREPARATIONS

Erythromycin is available in the following forms:—

(a) Oral tablets:	Erythromycin tablets (100 mg.) 'Ilotycin' tablets (100 and 200 mg.) 'Erythrocin' tablets (100 mg.)
(b) Oral suspension:	'Ilotycin pædiatric suspension' (100 mg. as the crystalline ethyl carbonate in 5 ml.) 'Erythrocin suspension' (100 mg. of the buffered stearate in 5 ml.)
(c) Parenteral preparation:	'Erythrocin lactobionate'. Ampoules contain 300 mg. or 1 g. in lactobionate
(d) Ointment:	'Ilotycin ointment'. 10 mg. per g. of ointment. Supplied in ½-oz. tubes

The recommended oral dose for adults is 0.3 to 0.5 g. six-hourly, making a total 24-hour dose of 1.2 to 2 grammes. The recommended daily dosage for children is 30 mg./kg. body weight, divided into four or six equal doses. Most patients tolerate the tablets well, but in children an oral suspension may be preferable. In severely ill patients who have difficulty in swallowing parenteral therapy may be used.

The recommended parenteral dose of 'erythrocin lactobionate' for both children and adults is from 2.2 to 4.4 mg. per kg. body weight (1 to 2 mg.

per lb.). This dose should be repeated at intervals of eight to twelve hours. On occasion, if the situation is urgent, higher doses may be used, but no single dose should exceed 500 mg. If practical, the intravenous route is to be preferred. The lactobionate is diluted with 20 ml. of water, or 5 per cent. dextrose solution, in the case of the 1-g. vial, or with 6 ml. in the case of the smaller 300-mg. vial. Saline must not be used for this initial dilution, as inorganic salts may cause precipitation of the active ingredient at this concentration. The resulting 5 per cent. solution contains 50 mg. of erythromycin per ml. and may be used undiluted for intramuscular injection. For intravenous therapy, however, further dilution to a 1 per cent. solution must be employed, and in this case either sterile dextrose or saline is suitable. The intravenous injection should be made over at least five minutes, as otherwise pain may be felt along the course of the vein. The solution may also be given through an intravenous drip, either by injecting it directly into the rubber tube, or by diluting it in from 100 to 500 ml. of dextrose or saline. If these precautions are observed, venous thrombosis does not occur.

Intramuscular injection must be made into a large muscle, as the solution is irritating and pain at the site of injection is common. Nevertheless, no cases of tissue damage have been reported.

Erythromycin administration should be continued for at least forty-eight hours after the temperature has returned to normal and all evidence of the infection has disappeared. It is probably wise to insist on a minimum course of five days. If improvement is not obvious by the end of a week, resistant organisms are likely to be present and further administration is not indicated except in patients with bacterial endocarditis, in whom response may be notoriously slow.

INTERACTION BETWEEN ERYTHROMYCIN AND OTHER ANTIBIOTICS

No satisfactory clinical evidence of synergism or antagonism between erythromycin and the other antibiotics is at present available. We must therefore rely on *in vitro* experiments, and the subject has been fully investigated by Manten (1954). He concludes that the action of erythromycin is synergistic with that of streptomycin and antagonistic to that of penicillin, whilst it has no interaction with either chloramphenicol or oxytetracycline.

Although it is notoriously dangerous to translate *in vitro* experience into clinical fact, Manten's work does suggest that if a combination of erythromycin with a bactericidal antibiotic is required, streptomycin and not penicillin should be used. It must be stressed, however, that normally erythromycin should be used alone, its inclusion in an 'antibiotic cocktail' being reserved for the treatment of a partially resistant organism or occasionally for patients with bacterial endocarditis (see p. 37). Cross-resistance does not occur between erythromycin and other antibiotics.

INDICATIONS

Erythromycin has a similar spectrum to penicillin, can be given by mouth,

and is practically free from toxic effects, so that it is tempting to employ it as an alternative to penicillin in all infections caused by gram-positive cocci. Such a policy had been followed for five months in a Chicago hospital when Lepper and Dowling with their colleagues (1953) found that 70 per cent. of *Staph. aureus* cultures obtained from a cross-section of the hospital population were erythromycin-resistant. As there is no cross-resistance between erythromycin and penicillin, this clearly demonstrates the rapidity with which this organism develops resistance to erythromycin. On the other hand, Grigsby *et al.* (1955) report from another hospital, where erythromycin had been in use for two years but had been limited to those patients in whom a definite indication, such as infection due to penicillin-resistant staphylococci, existed, that out of 148 strains of staphylococci, 133 were still sensitive. Consideration of these two articles demonstrates the wisdom of keeping back this new antibiotic to combat staphylococcal infections which are resistant to penicillin and other antibiotics, and which present a very serious therapeutic problem.

The main indications for erythromycin can be summarized as follows:—

(1) Infections due to *Staph. aureus* when the strain present has been proved *in vitro* to be resistant to other antibiotics.

(2) Infections due to *Staph. aureus* which have failed to respond clinically to penicillin and one of the broad-spectrum antibiotics.

(3) Infections due to other gram-positive cocci if a definite contraindication to penicillin therapy exists, such as the occurrence of penicillin sensitization.

(4) Diphtheria carriers in whom penicillin has failed to eradicate the organisms. That erythromycin may be very effective in the last context, has been shown by Blute (1954) and Forbes (1954).

Erythromycin is not indicated in the treatment of infections due to the gram-negative cocci, where penicillin is perfectly satisfactory and the problem of resistance is almost non-existent. Bacterial infections are better treated with chloramphenicol or one of the tetracycline group of antibiotics. Erythromycin may occasionally be indicated in the treatment of brucellosis due to the *suis* and *melitensis* organisms.

Its bacteriostatic properties make it unsuitable for use in bacterial endocarditis, at any rate by itself. In this disease, successes have been recorded when it is used in conjunction with other antibiotics, as in the case of staphylococcal endocarditis recorded by Johnson and Hurst (1954), in which success was achieved with a combination of erythromycin, streptomycin and tetracyline.

The use of the ointment should be confined to superficial skin infections due to gram-positive cocci, such as sycosis barbæ or impetigo, when cultures taken from the lesions show it to be superior to chloramphenicol.

CONTRAINDICATIONS

There are no specific contraindications to the use of erythromycin but, as

already stressed, it must not be used as the first line of defence in infections due to gram-positive cocci, tempting as this policy may seem, or sooner or later the appearance of a population of resistant staphylococci will prevent it fulfilling its main function, which is to treat infections due to this organism when all else has failed.

TOXIC EFFECTS

These are mild and few and far between. The commonest are diarrhœa and vomiting, but the relatively slight effect of erythromycin upon the bacterial population of the gut makes severe intestinal syndromes almost unknown, although pruritus ani has been observed. Whilst erythromycin does contain a nitrogen atom, this is contained in an amino and not a nitrobenzene group (as in chloramphenicol), and no serious bone marrow dyscrasias have been reported, although some depression in the white count has been recorded in very rare instances. As a precaution, blood counts should be carried out at regular intervals if administration is continued for more than ten days.

SUMMARY

Erythromycin is an excellent, non-toxic antibiotic with a spectrum of action very similar to penicillin.

It is active when given by mouth and is without cross-resistance to other antibiotics.

Bacteria and especially staphylococci do, however, develop resistance to it with about the same readiness as they do to penicillin.

Its main function is in the treatment of staphylococcal infections which have proved resistant to penicillin and other antibiotics, and if this function is to be preserved, it must be guarded zealously and only employed when a clear indication exists, lest the staphylococcal population should come to know it too well and this familiarity should finally breed contempt.

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NEOMYCIN

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THIS short review of neomycin is based upon our personal experiences with neomycin which we have been studying in the laboratory and in the treatment of approximately 300 patients during the past six years. In the main, our results are not at variance with other published studies.

ANTIBACTERIAL SPECTRUM

Neomycin has the widest antibacterial spectrum of any of the antibiotics (Waisbren and Spink, 1950a; Pulaski, 1953). It is effective against the majority of pathogenic gram-negative bacilli as well as virtually all strains of *Micrococcus pyogenes*. Table 1 shows the percentage of strains of common pathogens that are sensitive to a concentration of neomycin that we have found to correlate with a clinical response. Each of these 507 strains of bacteria had been pathogenic to a patient at the Milwaukee County General Hospital. It can be seen that *in vitro* 65 per cent. of these pathogens are sensitive to neomycin. It is the most effective agent *in vitro* against *Aerobacter aerogenes*, *Pseudomonas* species, *Micrococcus pyogenes* and *Salmonella*. The organisms against which neomycin is least effective are proteus, *Ps. aeruginosa*, *Pseudomonas* species and enterococci. It is of interest to note that in the case of *Pseudomonas* species, in spite of the fact that only 37 per cent. of the strains were affected by neomycin, it is the best drug that we now have available (Irwin *et al.*, 1953). It should be noted also that many strains resistant to the other antibiotics are sensitive to neomycin.

As it is relatively ineffective against the streptococcus, especially *Streptococcus viridans* and gamma streptococci, these relatively benign organisms usually predominate in infected lesions that are being treated with neomycin.

MODE OF ACTION

The important practical consideration regarding the mode of action of neomycin is that it is primarily bactericidal rather than bacteriostatic. In fact, it is the only antibiotic with a wide antimicrobial spectrum that is bactericidal. The tetracycline group of antibiotics and chloramphenicol have a wide dichotomy between the concentration at which they inhibit the growth of micro-organisms and that at which they actually kill them. Neomycin, on the other hand, actually destroys bacteria within a relatively short time after exposure and the concentration at which it does this is usually identical to that at which it inhibits growth (Waisbren and Spink, 1950a). In other words, the concentration of neomycin that will inhibit bacteria is usually sufficient to kill them.

BACTERIAL RESISTANCE

The important consideration regarding bacterial resistance to neomycin is the stability of organisms in regard to their sensitivity to its action. Mutant forms that are resistant seldom arise in cultures of bacteria that were initially sensitive (Waisbren and Spink, 1950a). In over 400 strains of *M. pyogenes* we have found only one resistant strain. In addition, we have been unable to demonstrate increasing resistance to neomycin while patients are being treated. This is in counterdistinction to experience with streptomycin in which organisms become resistant during therapy. In addition, to date we

Organism	No. of pathogenic strains tested	% inhibited by 3 μg./ml. or less of neomycin†	Neomycin rank among antibiotics*	Most effective antibiotic or combination of antibiotics	% inhibited by 3 μg./ml. or less of most effective antibiotics	% of strains resistant to the most effective antibiotics that were sensitive to neomycin
E. coli	77	71	3	Chlortetracycline	74	57
A. aerogenes	50	70	1	Neomycin	70	—
Proteus	77	36	4	Penicillin and chloramphenicol	43	44
Ps. aeruginosa	120	38	4	Polymyxin B and oxytetracycline	67	34
Pseudomonas species	51	37	1	Neomycin	37	—
M. pyogenes	100	99	1	Neomycin	99	—
Salmonella	13	77	1	Neomycin, tetracycline and oxytetracycline	77	—
Shigella	12	83	2	Chlortetracycline	92	0
Enterococcus (group D streptococcus)	8	63	3	Erythromycin	96	100
Significant totals	508	65	—	—	—	—

†The sensitivity of each organism to the various antibiotics was determined by the tube dilution method (Waisbren *et al.*, 1951a).

*In this study, chlortetracycline, oxytetracycline, tetracycline, penicillin, erythromycin, bacitracin, chloramphenicol, streptomycin, polymyxin B and nitrofurantoin were compared.

TABLE 1.—The *in vitro* activity of neomycin against pathogenic strains of bacteria isolated from patients at the Milwaukee County General Hospital.

have found no inhibitors similar to penicillinase that will inactivate neomycin (Waisbren *et al.*, 1951a,b).

TOXICITY

When the antimicrobial spectrum, mode of action, and bacterial resistance are considered together, we see that in neomycin we have a wide-spectrum agent that is bactericidal and to which there appears little likelihood of significant resistance occurring. Certainly, no other agent is comparable in these respects. Why then do we not have a panacea? In our opinion, the answer to this question is that neomycin is too toxic to be used parenterally, except in selected patients. Its renal toxicity is probably comparable to that of bacitracin and would not preclude its general use (Waisbren and Spink, 1950b). Not infrequently, however, it does make people deaf. Thus, before it is used parenterally, the physician must ask himself whether the situation is serious enough to risk this complication. Among the first 64 patients we treated by the parenteral route five became deaf, and since that time our incidence of deafness is at least 10 per cent. in patients who are given the drug by the parenteral route. Deafness caused by neomycin has been progressive. In no instance have we noted improvement after its onset, but it has not progressed to total loss of hearing in every case.

Renal damage is first manifested by albumin and casts in the urine. This is followed by an increase in nitrogen retention and by oliguria. In our experience, the renal damage has always been reversible if therapy was stopped when oliguria and nitrogen retention occurred, but the appearance of casts or slight albuminuria has not caused us to discontinue treatment.

It is important to emphasize that renal toxicity and nerve deafness have not been found after oral or topical application. No hæmopoietic depression or local sensitization has, as yet, been encountered.

DOSAGE AND METHODS OF ADMINISTRATION

Neomycin can be administered topically, intravenously, intramuscularly, intrathecally, intrapleurally, intraperitoneally, in joint cavities and by aerosol. Blood levels of approximately 5 μg. per ml. can be obtained by intramuscular injection, and levels of about 1 μg. per ml. follow oral administration (Waisbren and Spink, 1950b). We have repeatedly confirmed our original observation that neomycin given by the oral route results in demonstrable serum levels and therefore cannot agree that this drug is a so-called 'non-absorbable preparation' similar to phthalylsulphathiazole (Poth *et al.*, 1950). Table 2 shows the dosages we have used and how the material has been prepared for each method of administration.

INDICATIONS FOR PARENTERAL ADMINISTRATION

Parenteral administration of neomycin is rarely indicated, but the two following short case reports demonstrate the sort of situation in which we have found neomycin to be lifesaving:—

Case 1.—The patient was a 66-year-old white male who when first seen appeared acutely ill, was jaundiced, severely anæmic and had a rectal temperature of 105°F. (40.5°C.). He had been operated on for carcinoma of the prostate three months before and had been febrile ever since, the rectal temperature ranging from 100°F.

Method of administration	Daily dose and intervals at which it is given	Solvent	Volume
Intramuscular	0.5 g. 4 times a day	Sterile saline	1 ml.
Oral	0.5 g. 4 times a day (i.e. one tablet 4 times a day)	None	—
Intravenous	0.5 g. twice daily	Sterile saline	500 ml.
Topical for large areas of burn with secondary infection, or for exfoliation	2 g. daily	Distilled water or sterile saline	Dissolve in concentration of 1 mg. per ml. and apply thin single thickness dressings to exposed infected areas and keep moist.
Aerosol with or without intermittent positive pressure	0.25 g. twice daily	Sterile saline, 'alevaire', 'aerolone' or 3-4% phenylephrine	1 ml. in No. 44 DeVilbiss nebulizer—oxygen running at 6 litres per min. diverted through nebulizer when patient puts finger over opening of a Y tube as he takes a deep inspiration.
Intrathecal	20 mg. daily	Sterile saline	5 ml.
Intrapleural	0.25 g. daily	Sterile saline	10 ml.
Joint cavities	0.25 g. daily	Sterile saline	5 ml.
Intraperitoneal	1 g. daily	Sterile saline	300 ml.

TABLE 2.—The various methods of administering neomycin.

(37.8°C.) to 105°F. (40.5°C.). He had received full therapeutic doses of chlortetracycline, sulphadiazine, chloramphenicol, oxytetracycline, penicillin and streptomycin. When he came under our care a blood culture revealed the presence of a *Pseudomonas* organism. Sensitivity studies on this organism showed that it grew in 100 μg. per ml. of chlortetracycline, chloramphenicol, oxytetracycline, streptomycin, and penicillin. It was inhibited by 0.75 μg. per ml. of polymyxin B and 1.5 μg. per ml. of neomycin. Neomycin, 0.5 g., was given intravenously in 500 ml. of 0.9 per cent. sodium chloride and repeated at twelve-hour intervals. There was a clinical response in twelve hours. After three days of therapy by the intravenous route the neomycin was given intramuscularly, 0.5 g. four times daily for 11 more days. During this time the non-protein nitrogen rose from 35 to 56 mg. per cent. but the daily urinary output remained above 1,500 ml. The patient became afebrile, blood cultures were sterile, his jaundice disappeared and he became clinically well. Three weeks after the onset of therapy he began to complain of difficulty in hearing and at the end

of twelve months had become almost completely deaf. The non-protein nitrogen fell to normal within two weeks after completion of therapy. When the patient died two years later of a bleeding ulcer, no evidence of renal damage that could be attributed to neomycin was found.

This case exemplifies a situation where a patient was dying of sepsis due to an organism that was resistant both *in vitro* and clinically to all antibiotics except neomycin and polymyxin B. He was cured by the administration of neomycin but became deaf as a result.

Case 2.—The patient was an 18-year-old boy who had had a chronic otitis media for many years. Two weeks before admission he had developed a purulent meningitis which was treated at another hospital with penicillin, streptomycin, sulphadiazine and full therapeutic dosages of cortisone. He had made a prompt clinical response and had been discharged after being in hospital for a week. The night before admission, he became febrile and lapsed into a deep coma. Neurosurgical intervention revealed a cerebellar brain abscess and a blockage of the cerebrospinal fluid between the lateral and third ventricles. A tube placed in the lateral ventricle drained about 500 ml. of spinal fluid a day. Gram-stained smears of the cerebrospinal fluid revealed a small gram-negative bacillus but cultures showed no growth. In spite of treatment with chlortetracycline, penicillin and streptomycin, the oral temperature had been climbing to 106°F. (41.1°C.) each day. The concentration of sugar in the cerebrospinal fluid remained below 20 mg. per cent. It was felt that neomycin therapy was justified and 0.5 g. was given intravenously, four times daily. In addition, 5 mg. of neomycin and 5 mg. of polymyxin B were instilled in the spinal fluid daily. Streptodornase and streptokinase were placed in the lateral ventricle and the leakage of cerebrospinal fluid ceased (we assume the intraventricular block was dissolved by the enzyme action). After forty-eight hours of this therapy the cerebrospinal fluid sugar concentration continued low, even though the patient seemed a little better. A left radical mastoidectomy was done (no anæsthesia was necessary), a large thrombus was removed from the lateral vein and a cholesteatoma was removed. Gradual improvement followed. Neomycin therapy, both by the intravenous and intrathecal routes, was continued for three weeks and the fever gradually disappeared and the cerebrospinal fluid sugar became normal. The patient remained unconscious for an additional three months but then gradually became alert and rehabilitation was started. In the ensuing three years he has continued to improve and now is up and about on crutches and taking vocational rehabilitation. His hearing is definitely impaired but he is not completely deaf.

This patient's recovery can be attributed just as much to the brilliant surgery as to the chemotherapy but it exemplifies the type of situation in which we do not hesitate to use neomycin by all routes available.

Before the advent of erythromycin and parenteral chloramphenicol there appeared to be an increasing number of cases of severe sepsis due to *M. pyogenes* in which neomycin was the only antibiotic that was active against the causative strain. The combination of intravenous chloramphenicol and erythromycin, however, with possibly the addition of intramuscular bacitracin, now appears to take care of the majority of severe sepsis due to this organism. On the other hand, it is our conviction that a patient should not be allowed to die of an infection due to *M. pyogenes* without having received neomycin by the intravenous route. We hold the same opinion in regard to other severe bacterial infections that do not appear to be responding to therapy with the other antibiotics. It is our practice to inform the patient or his family of the risk of deafness due to neomycin before we use it, but deafness is not inevitable and in certain cases is undoubtedly a justified risk.

AEROSOL NEOMYCIN

We believe neomycin given by aerosol to be the most effective antimicrobial agent in the management of patients with chronic bronchitis, bronchiectasis and emphysema. In over 100 patients such treatment has resulted in a reduction of sputum, fever, cough and symptoms in the great majority. No toxicity has been observed. These excellent clinical results can be attributed to neomycin's wide spectrum, to its bactericidal mode of action and to its relative inactivity against *Streptococcus viridans* and gamma streptococcus. Given as outlined in table 2, neomycin apparently reduces the total bacterial flora in the respiratory tree, kills many of the pathogens and allows benign organisms to establish the predominant flora. Our usual procedure is to give a four-day course of neomycin in some bronchodilator preparation every four to six weeks to patients with chronic pulmonary disease. Intermittent positive pressure has not improved our results with this method of treatment. It should be emphasized that this is only one form of treatment to be used in these patients, and in the management of this difficult group of patients we continue to insist on postural drainage, abdominal supports, expectorants and abstinence from tobacco.

Two cases of lung abscess have been treated successfully with neomycin given by aerosol over a six-week period. Both patients were over 75 years of age and poor surgical risks. This certainly should not be considered the treatment of choice for this condition which usually responds best to surgery and parenteral antibiotics in massive dosages, but in debilitated patients who can tolerate neither surgery nor massive chemotherapy, neomycin given by aerosol is worth trying.

ORAL NEOMYCIN

The use of neomycin orally has been pioneered by Poth (1950), who was the first exponent of its use as a preoperative bowel preparation. It has been very satisfactory in this respect and certainly is the most effective agent yet used for this purpose. Poth has added a non-absorbable sulphonamide preparation to neomycin in order to cut down the bowel flora even further, but in our experience neomycin used alone is satisfactory (table 2). In hospitals in which postoperative diarrhœa due to *M. pyogenes* has become a serious problem, the use of oral neomycin to prevent the establishment of this organism in the gastro-intestinal tract is definitely indicated in all cases in which one of the tetracyclines or penicillin and streptomycin combined are going to be used (Barber, 1947).

Another important use of oral neomycin is in diarrhœa due to certain strains of *E. coli* and *Proteus morganii* (Wheeler and Wainermann, 1954). In these cases we have used the tablets in a dosage of 0.5 g. three times a day for adults, and about one-half this dose for children. The combination of neomycin in 'kaopectate' contains considerably less neomycin than this and, in our experience, sick children particularly cannot tolerate 'kaopectate'. Oral neomycin is also useful in the treatment of Shigella carriers who do

not respond to chloramphenicol. We have been able to return two patients who were chronic Salmonella carriers to institutions where they had been considered a public health menace, by giving them a ten-day course of 2 g. of oral neomycin daily. In both instances a similar course of chloramphenicol had been ineffective.

A final use of oral neomycin is to improve the tolerance of the patient to the tetracycline group of antibiotics when they have to be administered orally for long periods of time. In certain cases of bacterial endocarditis, osteomyelitis or chronic pyelonephritis, we have given one of these antibiotics in a dosage of 2 g. a day for as long as six weeks. We have found that these patients tolerate this regimen if neomycin is given concomitantly by the oral route. This is probably due to the fact that the neomycin prevents the establishment of *M. pyogenes* and certain strains of *Proteus* as the predominant micro-organisms in the bowel.

A discussion of oral neomycin would not be complete without emphasis being placed on the fact that the drug is absorbed and demonstrable in the blood stream after the administration of as little as 0.5 g. by mouth (Waisbren and Spink, 1950a; Poth *et al.*, 1950, 1951). Although as yet there have been no reports of toxicity following the use of oral neomycin, in two instances we have observed rather sudden rises in the concentration of non-protein nitrogen in patients who had received neomycin orally for one week. In one case, the situation reversed when the drug was stopped.

TOPICAL USE OF NEOMYCIN

The wide antimicrobial spectrum of neomycin makes it particularly useful as a topical agent. The practitioner who uses neomycin ointment in his cases of varicose ulcers will soon be convinced of its value in this situation. Although we have not had nearly as wide an experience as others, we share their high opinion of neomycin for skin infections such as infectious eczematoid dermatitis and pyogenic dermatitis (Livingood *et al.*, 1952; Kiles *et al.*, 1952). The solution in distilled water and the ointment are equally effective.

Another important use of topical neomycin is in severely burned patients who develop secondary infections in the involved areas. We have as yet encountered no cases of local sensitization after the use of topical neomycin.

OTHER USES OF NEOMYCIN

Neomycin in joint cavities.—We have used neomycin in joint cavities on three occasions when *M. pyogenes* was cultured after treatment with other antibiotics (table 2). In each case the drug was tolerated well, the cultures became sterile and the septic arthritis was cured. In two instances the wrist joint was involved and in the other case the knee joint was infected.

Neomycin in the pleural and peritoneal cavities.—Neomycin is tolerated well in the pleural and peritoneal cavities and in several instances has sterilized an empyema due to *M. pyogenes*. Neomycin will not affect tubercle

bacilli in the pleural cavity. In fact, even though it was discovered in a search for anti-tuberculous drugs, it is ineffective against most cases of tuberculosis (Waksman and Lechevalier, 1949; Waisbren and Spink, 1950b).

It has been difficult to assess the value of neomycin when it is placed in the peritoneal cavity, as the patients who were given such therapy simultaneously needed other forms of treatment. Our procedure has been to give patients with gross contamination of their abdominal cavity, daily irrigations by means of a catheter which during operation has been placed alongside the drains which have been left in place (table 2). This has proved a satisfactory adjunct to other more traditional therapy but should not be used in these cases to the exclusion of parenteral therapy with other antibiotics.

SUMMARY

Because of its wide antibacterial spectrum, its bactericidal rather than bacteriostatic activity, the lack of resistant mutants and the fact that it is relatively ineffective against streptococci that form normal body flora, *in vitro* neomycin is almost an ideal theoretical antibiotic. The fact that parenteral neomycin causes deafness in a not insignificant number of patients, however, makes it impossible to recommend its parenteral use in other than severely ill patients who have had adequate trial with other agents. On the other hand, it is our conviction that patients should not be allowed to die of severe sepsis, due particularly to *M. pyogenes*, without a trial of neomycin in full therapeutic dosage.

No serious toxic effects have resulted from the use of neomycin by other than the parenteral route, although the fact that neomycin is absorbed when given orally must be remembered when patients are given it by this route.

The greatest use for neomycin at present is when it is given by aerosol to patients with chronic pulmonary infections. In this situation it has been found to be safe and particularly efficacious.

The administration of neomycin by the topical, intra-articular, intrapleural, intrathecal, intraperitoneal and oral routes, each has applications and has been found to be well tolerated and safe.

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POLYMYXIN

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POLYMYXIN is the name applied to the group of antibiotics derived from the various species of *Bacillus polymyxa*. Five polymyxins designated by the suffixes A to E are known and all exert a powerful action against gram-negative bacteria. Polymyxins A, C and D are no longer used as they are liable to cause temporary injury to the renal tubules (Brownlee and Bushby, 1948; Bryer *et al.*, 1949; Brownlee *et al.*, 1952). Polymyxins B and E are free from any serious toxicity and are both suitable for systemic, oral and local administration (Jackson *et al.*, 1951; Swift and Bushby, 1951). Polymyxin B, in the form of the sulphate, is the type commercially available. This salt in the dry state is very stable; it is freely soluble in saline and in water and in solution in distilled water retains its potency for several months provided that the pH does not exceed 6.

The polymyxins were discovered independently and almost simultaneously in 1947 by Stansly and his colleagues in America and by Ainsworth, Brown and Brownlee at the Wellcome Laboratories in England. Earlier studies were made with polymyxins A and D and it was only later that polymyxins B and E were made available. By then the stigma of renal toxicity had become attached to the name polymyxin and thus mistakenly to polymyxins B and E. The absence of renal toxicity in these two strains is surprising when it is realized that nearly all other antibiotics of bacillary origin have this property.

Apprehension regarding toxicity and perhaps their limited antibacterial range have been responsible for their tardy acceptance. On account of their narrow antibacterial spectra polymyxins are not suitable for blindfold therapy but, in infections by susceptible micro-organisms, they are most valuable and powerful agents which are often superior in effect to the more commonly used antibiotics.

ANTIBACTERIAL SPECTRUM

Polymyxin is selectively active against the gram-negative bacilli except *Proteus* and is effective in smaller concentrations than other antibiotics (table 1). Polymyxin is pre-eminent in the treatment of *Ps. aeruginosa* infections, against which it is the most uniformly effective of all antibiotics. It is also highly effective against *E. coli*, *A. aerogenes*, *H. influenzæ*, *K. pneumoniæ* (Friedländer's bacillus) and the dysentery group, but exerts no action on *Proteus* or the gram-positive bacteria.

Its action, which is bactericidal, is remarkably rapid, with the result that organisms can only be made to acquire resistance with great difficulty and in practice do not do so. Bacterial sensitivity to polymyxin varies less from

strain to strain than sensitivity to other antibiotics, a feature which is of particular importance in the treatment of *Ps. aeruginosa* infections. In its narrow antibacterial range and its rapid bactericidal action, which is little

	Poly-myxin	Strepto-mycin	Chlortetra-cycline	Oxytetra-cycline	Chloram-phenicol
*Ps. aeruginosa**	0.1-3	100-200	3-50	3-6	25-100
*A. aerogenes**	0.2	12.5	1-12	1-6	
*E. coli**	0.1-3	7-25	5-25	0.5-3	5-25
*Sh. sonnei**	0.2	4	3-5	0.4-0.8	1
*Sh. flexneri**	0.2	8	3-5	1	1
*Sh. shigæ**	0.1	4			
*H. influenzæ**	<0.6	2.5-80	0.5-1	2	1
H. pertussis	0.05	0.5	0.5	0.5	1
K. pneumoniæ (Friedländer)*	0.3	4	1 3-5	1	
Salmonellæ	1-3		3-5		3-5
Proteus vulgaris	<80	3-30	10-100	10-100	
Streptococci	>80	2			

* Organisms against which polymyxin is therapeutically effective (1 μg. = 10 units of polymyxin).

TABLE 1.—Minimal effective concentrations (μg. per ml.) of five antibiotics.

impaired by large numbers of bacteria except in so far as higher concentrations are necessary, polymyxin resembles penicillin at the gram-positive end of the spectrum, and differs from the broad-range tetracycline antibiotics. When the infecting organism is equally susceptible to more than one antibiotic it is these differences in basic properties which will determine the suitability of an antibiotic for any individual case. The limited range, for instance, may be of particular advantage when there is risk from gross disturbance of the intestinal flora, which may be so dangerous in small babies.

Like penicillin, polymyxin is of greatest value in circumstances in which speed of action and a bactericidal, as distinct from a bacteriostatic, effect are demanded.

In the treatment of the chronic infected lesion the bactericidal action of polymyxin is of special value and may ensure success where other antibiotics fail. Thus, it has an important place in the chemotherapy of many gram-negative infections, in addition to its pre-eminence against *Ps. aeruginosa*.

The salmonellæ including *S. typhi* are highly sensitive to polymyxin *in vitro* (Brownlee and Bushby, 1948) but the antibiotic has a negligible effect on the course of the disease in man. *H. pertussis* is also highly sensitive *in vitro* but the response of whooping-cough is often disappointing.

In their studies on antibiotic synergism and antagonism Jawetz and his colleagues (1954) have found that polymyxin participates relatively infrequently in synergism and does not apparently cause antagonism. This they attribute to the apparent all-or-none effect of the drug. They did, however, find a moderate synergistic or additive action, when polymyxin was combined with streptomycin, chloramphenicol and oxytetracycline against *E. coli* and *A. aerogenes* but only rarely against *Ps. aeruginosa* and *Proteus*. From the point of view of practical therapeutics these findings are important. They suggest a means of eradicating organisms insusceptible to either antibiotic alone, and they offer a means of preventing the emergence of resistant organisms to streptomycin, chloramphenicol and oxytetracycline. Finally, they confirm that it is possible to use polymyxin in conjunction with these antibiotics, without risk of antagonism, for the treatment of mixed infections in which *Ps. aeruginosa* is present.

ADMINISTRATION AND DOSAGE

As polymyxin is not absorbed from the gastro-intestinal tract high oral dosage may be used with complete safety for the control of intestinal infections. In the treatment of systemic infections, parenteral injection is necessary. After intramuscular injection therapeutic concentrations are obtained in the blood stream within an hour and are maintained for four to six hours. Intravenous injection also gives high blood levels and at the same time avoids local tissue reactions (Pulaski and Fusillo, 1955). Diffusion across the blood-brain barrier is negligible so that adequate concentrations in the cerebrospinal fluid can only be obtained by intrathecal injection. For this purpose the lumbar, cisternal and intraventricular routes may be employed. As a precaution against the accidental introduction of gram-positive contaminants it is recommended that 2000 units of crystalline penicillin be added to solutions prepared for intrathecal injection. Concentrations in the urine after intramuscular administration are maximal after two hours and are about five times the height of those in the blood.

Dosage is as follows:—

Intramuscular: 3000 to 5000 units per lb. (6,600 to 11,000 units per kg.) of body weight every four to six hours; for adults 250,000 units. To minimize the effect of local reactions, injection should be made into alternate sites in the buttocks or thighs.

Intravenous: Total dose: 100 mg. in 250 ml. of 5 per cent. dextrose.

Oral: 20,000 units per lb. (44,000 units per kg.) body weight six-hourly.

Intrathecal: Total dose: 20,000 to 50,000 units according to age of child, daily or twice daily. The maximal dosage for adults is 100,000 units.

Local application to granulating surfaces: 100,000 units in 100 g. of base or in 100 ml. water.

Aural instillation: 10 per cent. solution in propylene glycol.

Nasal instillation: 0.5 per cent. solution in saline.

Conjunctival instillation: 1 per cent. ointment.

Subconjunctival injection: 2.5 to 5 per cent. solution in mydricaine and distilled water.

INFECTIONS OF THE URINARY TRACT

Polymyxin is highly effective against all gram-negative bacilli in urinary flora except *Proteus*. For infections with *Ps. aeruginosa* and *A. aerogenes* it is the antibiotic of choice. Polymyxin may be used alone for simple infections but, as both organisms are usually found in heterogeneous infections, a combination of polymyxin and a broad-spectrum antibiotic such as oxytetracycline is preferable for routine purposes. From the results of *in vitro* experiments on micro-organisms isolated from infected urines Neter and his colleagues (1952) predicted that this combination was likely to prove the most effective in the treatment of chronic urinary-tract infections. With this regime the whole range of bacteria found in chronic infections is covered and persistence of organisms such as *Ps. aeruginosa* and enterococci is prevented. Against coliforms the combination also has advantages by reason of its additive or synergistic action. In spite of its efficiency in eradicating sensitive bacteria, polymyxin, whether given alone or with other antibiotics, will have little permanent benefit if the causal abnormality in the urinary tract remains uncorrected. As a general rule therefore, antibiotic therapy will be coordinated with radical surgical treatment and if necessary may be continued for six weeks or more without ill effect.

In urinary infections of long standing associated with impaired renal function, Yow and Moyer (1953) advise that the total daily dosage should not exceed 20,000 units per kg. of body weight (or approximately 9000 units per lb.) and that if the degree of impairment is severe the dosage should be still smaller. Pharmacological studies, however, indicate that polymyxin is excreted more freely in the presence of renal damage so that lower rather than higher blood levels would be expected.

The type of case in which polymyxin will be used militates against dramatic results. As it is usually employed in infections such as chronic pyelonephritis and pyonephrosis, in which tissue destruction and chronic inflammatory changes are often associated with unrelieved obstruction, complete cure may even be impossible. In the more favourable case without gross structural lesions the urine becomes sterile in three to five days and full recovery may be expected (Pulaski and Rosenberg, 1954).

In acute urinary infections polymyxin is rarely required, as oral therapy with sulphonamides, oxytetracycline and chloramphenicol is so effective and convenient. In this type of infection polymyxin will be reserved for those cases which are resistant to standard treatment and for the occasional severe infection associated with septicæmia. A satisfactory dosage scheme for adults is 200,000 to 250,000 units of polymyxin by injection every six hours. For children the dosage should be proportionately less. For maintenance therapy in patients whose urine has been rendered sterile 200,000 units may be given every eight hours.

INFECTIONS OF THE ALIMENTARY TRACT

Dysentery.—Polymyxin is bactericidal to organisms of the Shigella group

and is particularly effective in eradicating both *Sh. flexneri* and *Sh. sonnei* from the stools (Ross *et al.*, 1949; Kagan *et al.*, 1951). It is no more effective, however, in controlling the symptoms of acute enteritis than the sulphonamides, streptomycin or chloramphenicol. At present its chief value lies in the treatment of chronic infections and in symptomless carriers who have proved resistant to standard therapy. Liebermann and Jawetz (1951) have found that a ten-day course of polymyxin in a daily oral dosage of 200,000 units per kg. of body weight (or approximately 90,000 units per lb.) produces bacteriological cure in 87 per cent. of such cases. By comparison, they obtained a cure rate of only 63 per cent. using various combinations of sulphonamides with streptomycin and chlortetracycline and chloramphenicol. It is interesting that the polymyxin-treated patients had already failed to respond to other forms of treatment and in most of them the organism was eradicated within five days. In their cases the infecting organism was *Sh. flexneri*, but similar results have been obtained in those due to *Sh. sonnei* by Ross and his colleagues (1949), which is important as this organism is the more common and the more difficult to eradicate.

Pyocyaneus enteritis.—Reports on the use of oral polymyxin in enteritis due to *Ps. aeruginosa* by Kagan and his colleagues (1951) and Mills and Kagan (1954) indicate that it is the best and often the only effective remedy. As a rule the organism rapidly disappears from the stools, even in cases of long duration. In neonatal epidemics of gastroenteritis caused by this organism polymyxin is effective not only in acute cases but also in clearing the stools of carriers, whether they be nurses or infants.

Infantile gastroenteritis.—In infantile gastroenteritis the results of polymyxin therapy are variable (Brownlee, 1949) and apparently bear little relation to the presence or absence of the causative organism.

MENINGITIS

Meningitis caused by gram-negative bacilli, though uncommon, is more frequent than in the past, and as a result of the widespread use of broad-spectrum antibiotics the number caused by insensitive organisms such as *Ps. aeruginosa* is increasing (Alexander, 1952). Of the gram-negative organisms encountered in meningitis *H. influenzæ*, *E. coli* and *Ps. aeruginosa* are highly sensitive to polymyxin. The treatment of these forms of meningitis does not differ in principle from that of other purulent meningitides. The success of therapy depends upon early diagnosis and early and optimal chemotherapy.

E. coli meningitis.—In meningitis caused by *E. coli*, which is a significant cause of death in the neonatal period, there are several antibiotics from which a choice has to be made. Of these chloramphenicol, oxytetracycline, streptomycin and polymyxin have been used. Although the number of recorded cases has been few, polymyxin appears to be the most effective. Ebsworth and Leys (1951) record the case of a baby who recovered. This infant, aged ten days, was treated for thirteen days with chloramphenicol

and subsequently, in view of the poor response, with polymyxin for five days. A similar case of my own responded well with complete recovery to treatment solely with polymyxin by lumbar injection (20,000 units daily) and intramuscular injection.

Pyocyaneus meningitis.—Polymyxin is the only antibiotic which is consistently and adequately effective against *Ps. aeruginosa* and therapeutic in practice. In the reports on its use in this condition polymyxin has rarely been the first antibiotic employed, the infection so often occurring as a complication of some other condition such as chronic mastoiditis or head injury. Inevitably there has been delay in starting correct treatment; as a result the subsequent course of the illness has been stormy and interrupted by relapse necessitating prolonged intrathecal therapy (Schoenbach, 1949; Jawetz, 1952; Trapnell, 1954). With more prompt bacteriological diagnosis there appears to be no reason, apart from the persistence of an underlying focus of infection, why the disease should not be more rapidly cured.

H. influenzæ meningitis.—The superior bactericidal effect and the proven therapeutic value of polymyxin in this disease (Kagan, 1949; Swift and Bushby, 1951) warrant serious consideration in any attempt to improve the results. Controlled trials comparing polymyxin with other forms of antibiotic therapy have not been made so that it is not possible at present for any particular regime to be claimed as the best. My own practice, which is based primarily on the need for immediate optimal therapy and secondarily on the desirability of avoiding unnecessary intrathecal injections, utilizes both polymyxin and chloramphenicol. For initial control of infection reliance is placed on polymyxin on account of its superior and more rapid bactericidal activity irrespective of the influence of host or bacteria. The antibiotic is given intrathecally in a dosage of 20,000 to 50,000 units daily (or twice daily in very severe cases) for two to three days, in addition to six-hourly intramuscular therapy. By this means delay in obtaining optimal concentrations at the site of infection brought about by vomiting, rejection of doses or slow absorption is avoided. After 48 to 72 hours, when clinical improvement becomes apparent and the cerebrospinal fluid has been sterilized, oral chloramphenicol alone is continued in order to dispense with further intrathecal injections. The therapeutic results have been uniformly satisfactory. Even in the absence of any controlled comparison with other regimes this method is recommended not only on the ground of efficacy but also on those of convenience.

MISCELLANEOUS SURGICAL INFECTIONS

Polymyxin is the only effective antibiotic in the treatment of wounds and cases of osteomyelitis which have become infected by *Ps. aeruginosa.* The nature of the lesion and the presence of devitalized tissues may necessitate prolonged systemic therapy but, in spite of these adverse conditions, the infection can usually be eradicated.

Granulating surfaces and burns.—For the prophylaxis and treatment of

Ps. aeruginosa infections of burns and granulating surfaces topical applications of polymyxin are highly effective (Pulaski *et al.*, 1949). Jackson and his colleagues (1951) found that 0.1 per cent. polymyxin cream applied daily eliminates the organism from established infections in the majority of cases. Used prophylactically the antibiotic greatly reduces the incidence of burns colonized by *Ps. aeruginosa* and coliform bacilli, and materially hastens the healing time of full-thickness skin-loss burns. At the same time they noted a significant improvement in the number of complete graft takes. On the strength of their results they recommend that a cream containing polymyxin in addition to penicillin should be used for the routine local treatment of burns.

INFECTIONS OF THE EAR AND ANTRA

In infections by *Ps. aeruginosa* of the nasal sinuses and ear polymyxin is the antibiotic of choice. In those due to other gram-negative bacilli alternative antibiotics are available which will be used in preference. For superficial infections instillation of a 10 per cent. solution of polymyxin in propylene glycol into the ear has been found by Farrar (1954) to be effective in eradicating pyocyaneus and, with less certainty, coliform organisms. For infections of the sinuses a 0.5 per cent. solution of polymyxin in saline is satisfactory (Jawetz, 1952). When the infection is deep seated and of long standing, as is usually the case in infections by gram-negative micro-organisms, superficial application alone may not penetrate throughout the infected tissues. Reliance must then be placed on systemic therapy either alone or in addition to local applications.

As there is a tendency for insensitive organisms such as *Proteus* or the gram-positive cocci to emerge during polymyxin therapy bacteriological surveillance is important. Failure of treatment from this cause may be obviated by the simultaneous administration of the appropriate broad-spectrum antibiotic.

OPHTHALMIC INFECTIONS

The outstanding indication for polymyxin therapy in infections of the eye is in the treatment of those due to *Ps. aeruginosa*. The majority of infections by other gram-negative bacilli are amenable also to the broad-spectrum antibiotics which will generally be used in preference. Ainslie (1953) obtained satisfactory results in severe *Ps. aeruginosa* infections by subconjunctival injection and topical application. For injection he used 0.2 to 0.25 ml. of a solution containing 1,000,000 units of polymyxin in 0.5 ml. of mydricaine and 0.5 ml. of distilled water. With this dosage some patients experienced pain about two hours after injection, for which analgesics were required. Fraser (1953) and Macdonald (1953) also obtained cures in unfavourable cases, using subconjunctival doses of 50,000 and 25,000 units. Pain with these smaller doses appears to have been insignificant or absent. Twice-daily irrigation with a 1 per cent. solution of polymyxin was also employed in these cases. To combat secondary polymyxin-insensitive

invaders, Ainslie recommends the application of 1 per cent. chlortetracycline ointment in patients receiving polymyxin.

TOXICITY

Polymyxins B and E are free from any serious toxicity (Swift and Bushby, 1953) and therein differ from polymyxins A, C and D which are no longer made. The side-effects associated with polymyxins B and E are at the worst annoying to the patient and not sufficient to contraindicate their use. With polymyxin B transient pain and inflammation at the sites of injection are not uncommon. Often there may be low-grade fever and general malaise while the drug is being administered. The persistence of fever in a patient whose infection, as judged by other criteria, has been controlled may thus be due to the drug. Polymyxin E causes less pain—no more than an injection of penicillin—and is less often associated with fever than polymyxin B. It is therefore the preparation of choice.

Local inflammation, which is more frequent in adults than children, seems to be dependent upon the size of individual intramuscular injections. Intravenous injection overcomes this disadvantage and, provided that the injection is made slowly, is apparently free from risk. The lesions do not progress to necrosis, and resolve spontaneously in twenty-four to forty-eight hours. They are attributed to the length of the constituent peptide chains in the polymyxin molecule (Swift and Bushby, 1953) which act on the cells in a manner similar to those released naturally in tissues injured by burns or infection (Spector, 1951).

Both polymyxins B and E may cause a sensation of itching, of the face and elsewhere, flushing of the face and occasionally ataxia (Kagan *et al.*, 1951). These again are transient phenomena which disappear rapidly on withholding treatment and are more common in adults than in children. Experimental evidence indicates that they are due to release of histamine (Bushby and Green, 1955). Kagan and his colleagues (1951) have found that antihistamine drugs afford relief.

The nephrotoxic effect of polymyxins A, C and D, which attracted so much publicity in the past, is not found with polymyxins B and E. It is now believed that this difference is another manifestation of their different molecular weights and of the length of their peptide chains. The nephrotoxic strains have low molecular weights and short-chain peptides; they do not in consequence cause significant reaction at the sites of injection. The injury to the tubules, being reversible and transient, differs from the permanent damage to the eighth nerve caused by streptomycin.

Local applications of polymyxins B and E in therapeutic concentrations do not cause injury to tissue cells. Cruikshank and Lowbury (1952) have found that concentrations in excess of 0.2 mg. per ml. and 2 mg. per ml. of polymyxins B and E respectively are required to inhibit the growth of tissue culture cells. In this respect the polymyxins, and particularly polymyxin E, are comparable to penicillin and in general less toxic than the broad-

spectrum antibiotics. It is interesting that these authors also found that polymyxin in non-toxic amounts has a stimulant action on the growth of epithelial cells. Applied to the skin polymyxin has little tendency to induce hypersensitivity, though more widespread trial is necessary before the true incidence can be known.

Intrathecal, intracisternal and intraventricular injections of polymyxins B and E in correct dosage are without ill effects. High dosage is liable to cause non-specific meningeal irritation of comparable severity to that caused by penicillin or streptomycin and excessive dosage of polymyxin must likewise be avoided.

Teng and Johnson (1953) have recorded convulsions in a successfully treated neonate suffering from *E. coli* meningitis. This infant was given 50,000 units intracisternally and it is doubtful whether the convulsion can be wholly attributed to polymyxin.

CONTRAINDICATIONS

In recommended doses there are no serious toxic effects to contraindicate the systemic use of polymyxins B and E.

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BACITRACIN

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An excellent article on bacitracin by Maxwell Finland and Samuel Wright appeared in the December 1953 issue of *The Practitioner*. The purpose of the present contribution to this symposium on antibiotics is to stress certain of the points mentioned in the previous article and to bring the reader up to date on more recent experiences with bacitracin in the treatment of infections, particularly with regard to the safety and efficacy of its systemic administration.

In Finland and Wright's review the authors described the discovery and the production of bacitracin in the departments of surgery and biochemistry of the College of Physicians and Surgeons of Columbia University. Soon after its discovery the chemical structure of bacitracin was studied by Craig and his associates (1949) at the Rockefeller Institute and later by Newton and Abraham (1950) in England. These studies were made on some of the early commercial preparations of bacitracin. The latter observers reported a similarity between bacitracin and an antibiotic obtained independently in Great Britain which had been called 'ayfivin'. They proved that the two antibiotics were essentially similar and proposed that the name 'ayfivin' be abandoned and that the name 'bacitracin' be retained.

The unit of activity for bacitracin was chosen for convenience, with reference to its activity for Group A hæmolytic streptococci. Craig *et al.* (1952) estimated that the theoretical potency of 'pure' bacitracin approximates 66 units per mg. Commercial preparations now available contain more than 50 units per milligram.

ANTIBACTERIAL SPECTRUM

Bacitracin has a wide range of antibiotic activity for streptococci, both hæmolytic and nonhæmolytic, in the aerobic, microaerophilic and anaerobic groups, for all the staphylococci (micrococci), and for the clostridia—including the neurotoxic *C. tetani* and the myotoxic clostridia of the gas gangrene group. The gram-negative cocci are particularly susceptible, but bacitracin is weak against the aerobic gram-negative rods. The spectrum is revealed in table 1 (Meleney and Johnson, 1949).

DOSAGE

When bacitracin is used locally, rapid control of infections due to susceptible organisms is usually obtained by the application of solutions containing 500 units per ml., or of ointments containing 500 units per gramme. Generalized infections due to susceptible organisms are usually brought

under control by the intramuscular injection of 10,000 to 20,000 units (or 200 units per kg. of body weight in children) every six to eight hours in a concentration of 10,000 units per ml. Only rarely, if ever, is it necessary to

Organisms	Sensitive to bacitracin (in units)	Resistant to bacitracin (in units)
Aerobic bacteria:		
β hæmolytic streptococci:		
Groups A, B, C, F, G	0.025-0.005	
Group D	3-0.008	
Nonhæmolytic streptococci	3-0.025	
Pneumococci	0.1-0.002	
Staphylococci (coagulase-positive)	5-0.05	
Other micrococci:	5-0.008	
C. xerose	0.005-0.003	
C. diphtheriæ	0.015-0.004	
N. meningitidis	0.01	
N. gonorrhœæ	0.006	
B. anthracis	0.5-12.5	
B. subtilis group		50
E. coli		50
A. aerogenes		50
A. cloacæ		50
Proteus		50
Ps. aeruginosa		50
B. alkaligenes		50
S. typhosa		50
Sh. alcalescens		50
Flavobacterium (New Orleans strain)	0.0025	
H. influenzæ Type B	0.63	
Anaerobic bacteria:		
Cl. welchii	0.025-0.002	
Cl. septicum	0.01-0.002	
Cl. sordellii	0.01-0.005	
Cl. novyi	0.01	
Cl. tetani	0.01-0.006	
Cl. histolyticum	0.025-0.004	
Hæmolytic streptococci	0.01-0.001	
Nonhæmolytic streptococci	0.1-0.005	
Micrococci	0.5-0.005	
Diphtheroids	0.003	
Actinomyces israeli	0.075-0.005	
T. pallidum (Reiter strain)	0.004	
Fungi:		
Monilia albicans		50
Cryptococcus hominis		50
Nocardia asteroides		50

TABLE 1.—Antibacterial spectrum of bacitracin.

exceed a total dose of 80,000 units in twenty-four hours in adults and, because of the presence of a nephrotoxic factor (see p. 58), the total daily dose should never exceed 100,000 units, or 2 g. of the lyophilized powder. Because of pain at the site of injection, it is advisable to dissolve the powder in 2 per cent. procaine in saline or 1.5 per cent. monocaine hydrochloride. The sites of injection should be rotated through three or four different areas in twenty-four hours. The slow elimination of bacitracin makes it unnecessary to give it more often than every six to eight hours.

Bacitracin is well tolerated in body cavities, such as the pleura, the pericardium, the peritoneum, and the joints, as well as in the subarachnoid space of the cord and brain and in the ventricles of the brain, in concentrations of 500 to 1000 units per ml. It may therefore be used prophylactically in those areas after surgical operations, to minimize the danger of infection from any contamination of the operative field either from within or from without. In the peritoneal cavity after resection of any part of the gastro-intestinal tract, I have been in the habit of using 20,000 units of bacitracin in 20 ml. of saline containing 0.5 to 1 per cent. neomycin. These antibiotics have a synergistic action and together, perhaps better than any other combination, they cover the whole gastro-intestinal flora (Meleney and Johnson, 1953a). If sprayed on the operative field, the solution containing these antibiotics will reach any contaminating bacteria in high concentration and will render such organisms less capable of producing an infection. Although such locally applied antibiotics are absorbed from a closed body cavity and thus become systematically distributed, I have never seen any evidence of toxicity from these doses.

TOXICITY

The reports of nephrotoxicity of the first preparations of bacitracin made by the deep-tank method (e.g. Michie *et al.*, 1949) led to the statement appearing in many subsequent reports that bacitracin, whilst lifesaving in many cases, should only be used as a last resort because of its nephrotoxicity (Goodman and Gilman, 1955). Little consideration has been given to the fact that these reports of toxicity were made on studies of early lots. Since then the toxicity has been greatly reduced and the Food and Drug Administration specifications have been raised to give a wide margin of safety.

The first commercial preparations of bacitracin were made by surface growth of the organisms on soybean agar with extraction of the antibiotic by means of butanol. These early preparations contained many impurities which were carried over from the media and from other by-products of manufacture. Gradually these impurities were eliminated and a highly soluble, faintly yellowish powder was obtained in lyophilized form which could be readily dissolved in water or saline and then injected.

The first clinical application of bacitracin was made with the crude filtrates from cultures of the organisms, with a laboratory preparation concentrated 100 times, and with the early commercial preparations mentioned above. All of these gave striking clinical results when applied to local surgical infections (Meleney and Johnson, 1947). Little or no evidence of toxicity appeared in these early trials.

Routine studies with the early commercial preparations were made in the department of pharmacology at Columbia University, College of Physicians and Surgeons, and no untoward effects were demonstrated until very large doses had been administered. These effects were limited to evidence of swelling of the tubular epithelium of the kidneys. On the basis of this

experience bacitracin was then cautiously administered by intramuscular injection to human beings. Doses were gradually increased, with every indication of safety, up to 50,000 units every six hours, although clinical results were obtained with doses 1/10 to 1/5 of these amounts. Clinical data which clearly indicated the value of this antibiotic in controlling surgical infections gradually accumulated (Meleney *et al.*, 1948).

In the meantime, however, several pharmaceutical houses had undertaken the commercial production of bacitracin and a way was finally found to produce the antibiotic in large quantity in deep tanks. When this product had been obtained in lyophilized form and was ready for clinical use, the doses which had been shown to be safe with the earlier preparations were used at the very outset. It was then found that this new material gave evidence of greater nephrotoxicity than the material produced by the surface-growth method. Extensive studies were then undertaken to determine the nature of this nephrotoxic factor and to discover if possible the reason for the wide differences in different manufactured lots. Standards had been set by the Food and Drug Administration for the potency and the minimal toxicity which had been thought to give an adequate margin of safety but, with the clinical and laboratory reports that began to appear, it was thought advisable to raise these standards in order to have a wider margin of safety. When this had been done, the systemic administration of bacitracin was renewed with restored confidence in its safety (e.g. Meleney, Johnson and Teng, 1952; Meleney and Johnson, 1953b).

The variation in toxicity has now been adequately explained by Codington (1955) who has confirmed the work of Craig and his associates (1952) and of Lockhart *et al.* (1954) that the commercial preparations of bacitracin contain three, or possibly five, different polypeptides varying somewhat in their composition. The antibiotic virtues of bacitracin are due principally to the major component, called bacitracin A. Some preparations, however, contain a considerable amount of an inactive degradation product, called for convenience bacitracin F. Whilst bacitracin F has lost the antibiotic activity found in the major factor, it has retained the nephrotoxicity. Manufacturers are now producing bacitracin with maximum content of bacitracin A and minimal content of bacitracin F. This measures up to the higher standards of assay and lower levels of toxicity now required by the Food and Drug Administration.

INDICATIONS

Bacitracin seldom, if ever, produces allergy and it should be used instead of penicillin whenever the patient gives any indication of penicillin allergy. Bacitracin is not inactivated by the penicillinase-producing secondary contaminants such as many of the gram-negative aerobic rods which often appear in mixed infections. Therefore bacitracin is likely to be more effective in mixed infections such as ulcers, burns or accidental wounds.

Bacitracin will often abort furuncles and shorten the course of carbuncles by the direct injection into the centre of the lesion of a small amount of a

solution containing equal parts of bacitracin, 1000 units per ml., and 2 per cent. procaine. If there is a wide area of induration around the central necrosis of a carbuncle, this solution may be injected around the periphery and will generally stop its farther spread. Abscesses will often resolve after three to four days by aspirating the pus and replacing in the cavity a smaller amount of this solution, thus obviating the necessity for a surgical incision.

Bacitracin is the antibiotic of choice in progressive bacterial synergistic gangrene, in which it obviates wide excision of the lesion, and in cases of undermining burrowing ulcer after excision of the undermined margins. Many staphylococci have become resistant to penicillin and the tetracyclines but are sensitive to bacitracin. Bacitracin should be used in such cases, particularly in fulminating infections with septicæmia, such as acute hæmatogenous osteomyelitis in which early administration may prevent the breakdown of bone. It is the antibiotic of choice in neurosurgical infections due to susceptible organisms. Prophylactically it may be used in all clean neurosurgical operations, as it is well tolerated by the brain tissues and it is generally potent against the organisms likely to produce wound contamination during long surgical procedures with the exposure of brain tissue.

One should not wait and use bacitracin only as a last resort when other measures have failed. The earlier an effective antibiotic is used in the course of any infection, the more likelihood there will be of a rapid control of the infectious process. If the organisms causing any serious infections are found by preliminary sensitivity tests to be susceptible to bacitracin, this antibiotic should be used as early as possible in the course of the disease.

Good news travels less rapidly than bad news and, although there have been many reports of the efficacy and safety of the systemically administered bacitracin since the early reports of its toxicity, it is well for the medical profession to be reminded again that bacitracin has been accepted by the American Medical Association's Council on Pharmacy and Chemistry (1954).

PRECAUTIONS IN THE SYSTEMIC USE OF BACITRACIN

There are no definite contraindications to the systemic use of bacitracin, but it should be administered with caution to patients with threatened renal failure or patients with heavy albuminuria or with a high blood urea nitrogen (over 25 mg. per cent.). Finland and Wright (1953) have outlined the precautions which I have always advocated. When these are followed, no untoward results need be anticipated and any effect on the kidneys is transient and reversible.

In addition to the precautions regarding dosage which I have already discussed, I should like to stress the following:—

(1) *Fluid intake and output.*—Fluids should be forced to 2,500 ml. or more a day in adults, with corresponding amounts for children. Intake and urinary output should be measured accurately every day. ***This is the most important feature of careful administration.*** The daily urinary output should be around 1000 ml. If it falls below 600 ml. a day, with a fluid intake of

2,500 ml., it would be wise to discontinue the bacitracin except in desperate circumstances.

(2) *Laboratory controls.*—The urine should be examined before beginning bacitracin treatment. It should be re-examined every third or fourth day thereafter for the presence of albumin, casts, and cellular elements. These may be expected to appear on the second or third day of treatment and to reach a low peak on the fifth to the seventh day and then to decline with continued treatment. The blood urea nitrogen often shows some variability during treatment, but this test is not essential unless there is oliguria.

(3) *Other side-effects.*—Loss of appetite may occur and in some patients this may go on to nausea or vomiting. This may often be controlled by the administration of 25 mg. of dimenhydrinate or chlorpromazine before each dose of bacitracin.

SUMMARY AND CONCLUSIONS

Bacitracin is now safe for systemic use. It is a potent agent against all of the severe coccal and clostridial infections, many of which have become resistant to penicillin and the tetracyclines. Primary hypersensitivity reactions to bacitracin are rare and allergic manifestations are practically nil.

Bacitracin is bactericidal and not simply bacteriostatic, and is therefore of particular value in infections connected with surgical procedures.

Certain types of infection in which bacitracin is to be preferred over other antibiotics have been mentioned.

Dosage schedules have been outlined and should be strictly followed.

Particular care should be taken to ensure a minimal intake of 2,500 ml. of fluid a day for an adult during systemic bacitracin administration. If the urinary output approximates to, or exceeds, 1000 ml. daily, there need be little fear of nephrotoxicity.

'Benemid' should never be used in conjunction with bacitracin.

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A GUIDE TO ANTIBIOTIC THERAPY

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For obvious reasons the accompanying table is presented with considerable trepidation. Its brevity gives no opportunity for discussion, nor is there any reference to prophylaxis: e.g. the administration of penicillin before a dental operation in a patient with rheumatic heart disease. In general, however, it may be said that the safer forms of treatment have been suggested and that the use of the broad-spectrum antibiotics has been restricted on account of their sometimes serious and often unpleasant side-effects. It is obvious, however, that in the special case, e.g. a sensitized patient, even penicillin can become exceedingly dangerous.

The treatment of tuberculosis is conducted by the specialist and is in any case too complex to tabulate. Similarly in venereal disease, although the immediate treatment is often simple enough, I feel that on general grounds the diagnosis and management of the case is best left to the expert whenever possible.

Finally it may be stressed that with unusual cases, failing to respond as expected to the obvious treatment, bacteriological investigation is the soundest guide for future therapy and is best carried out in a properly equipped hospital; in the treatment of some conditions, e.g. acute meningitis or generalized staphylococcal infection, such management is essential.

Abbreviations: pen. = penicillin; str. = streptomycin; tetra. = one of the tetracyclines (chlor-, oxy- or tetra-cycline); chl. = chloramphenicol; erythro. = erythromycin; sulph. = sulphonamide; sens. = sensitive; rt. = resistant; I/M = intramuscular; I/V = intravenous; I/T = intrathecal.

Condition and Type	Drug, Dosage and Course	Remarks
Staph. infection		
(1) Generalized	(1) Pen. 0.5 mega t.d.s. for 3 weeks if sens. If rt. to pen., tetra. 0.5 g. 6-hourly, or erythro. 0.5 g. 6-hourly, or both.	(1) Sens. test essential. Surgical treatment of abscess, etc., if present.
(2) Cutaneous	(2) Test sensitivity: in local treatment avoid drug capable of systemic use.	(2) Disinfect skin round lesions with spirit or cetrimide until healed. Need for systemic treatment varies with case and lesion.
(3) Superinfection, e.g. enteritis	(3) Erythro. 0.5 g. 6-hourly for 5 days, or parenteral 0.25 g. 6-hourly.	(3) Fluid replacement. Stop existing antibiotic therapy.

Condition and Type	Drug, Dosage and Course	Remarks
Upper respiratory tract infection		
(1) Sore throat	(1) Procaine pen. 0.3 mega for 7-10 days, or sulph.	(1) Drugs only needed in severe cases of infection with *Str. pyogenes*, or old rheumatic fever case.
(2) Otitis media	(2) Pen. 0.5 mega *at once*, then oral pen. if necessary.	(2) *Immediate* treatment necessary to prevent later deafness.
(3) Acute sinusitis	(3) Pen. 10,000 units/ml. in spray or drops; with fever, also pen. I/M.	
Pneumonia		
(1) Pneumococcal, *Str. pyogenes*	(1) Pen. aqueous + procaine, 0.3 mega/day, or sulph. full dose.	Culture if possible to detect unusual types, especially during influenza epidemic and with poor response.
(2) *H. influenzæ* post-influenzal	(2) Tetra. 1 g. daily.	Duration of treatment varies with case.
(3) Staphylococcal	(3) If sens., pen. 0.5 mega t.d.s., or tetra. or erythro. 2 g./daily.	
(4) Friedländer	(4) Str. 2-3 g./day, or tetra. 1-2 g./day.	
Bronchial infection		
(1) (*a*) Chronic	(1) (*a*) Prolonged treatment inadvisable.	(1) Infection usually pneumococcal or *H. influenzæ*.
(*b*) Acute exacerbation	(*b*) Pen. or tetra, as in pneumonia.	
(2) Pertussis	(2) Tetra. 35 mg./kg.	(2) Of value during first week only.
Endocarditis		
(1) *Str. viridans*	(1) Pen. 2-4 mega/day for 4-6 weeks.	(1) If pen. and str. fail, tetra. + pen. rarely successful.
(2) *Str. fæcalis*	(2) Pen. 10-20 mega/day + str. 2 g./day for 6 weeks.	(2) Tetra., chl. and erythro. useless.
Acute meningitis		
(1) Meningococcal	(1) Sulphadiazine or sulphatriad full dose.	All forms: continue 1 week after C.S.F. sterile. (1) If very severe, add pen., 1 mega 2-hourly I/M.
(2) Pneumococcal (or *Str. pyogenes*)	(2) Pen. 1 mega I/M 2-hourly or 0.5 mega I/M t.d.s. + 20,000 units I/T b.d.s. (addition of tetra. or chl. contraindicated).	(2) With patient sensitive to pen., chl. 100 mg./kg. daily may succeed.
(3) *H. influenzæ*	(3) Chl. 100 mg./kg./day, or str. 45 mg./kg. I/M + 50-100 mg. I/T daily + sulph.	(3) *C.S.F. level of* 10 μg./ml. *of chl. needed.* With vomiting, str. better.
(4) Others	(4) Test sensitivity.	(4) Bacitracin, neomycin and polymyxin may be given I/T.

CONDITION AND TYPE	DRUG, DOSAGE AND COURSE	REMARKS
Alimentary infections		
(1) Enteric fever	(1) Chl. 2 g./day for 4-5 days, then 1 g./day for 7-10 days.	(1) Chl. useless in fæcal carrier.
(2) Bacillary dysentery	(2) If sens. sulphadiazine or phthalylsulphathiazole. If rt. to sulph., oral str. 3 g./day or tetra. 1-1.5 g./day.	
(3) Infantile gastro-enteritis.	(3) Isolate pathogen and test.	(3) *Fluid replacement essential.*
(4) Peritonitis	(4) Tetra. 1-2 g./day I/V, or pen. 2 mega+str. 2 g./day I/M.	(4) Also fluid and electrolyte replacement.
Urinary infections		
(1) *E. coli*	(1) Alkali and sulph., during culture and sensy. test.	Infection, especially if recurrent, often due to obstruction or other abnormality. Effect of drugs only temporary and follow-up essential.
(2) Gram+cocci	(2) Pen. usually.	
(3) Proteus	(3) ? Pen. 0.5 mega t.d.s. ? 'Furadantin' 5-8 mg./kg.	(2), (3) and (4) Antibiotic therapy should be limited to severe, intractable infections, and to cover surgery.
(4) *Ps. aeruginosa*	(4) ? Str. 2-3 g./day for 2 days. ? Polymyxin B or E 1.5-2 mg./kg./day, in 4-hourly I/M dose.	
Actinomycosis	Pen. 0.5 mega. t.d.s. for 4 weeks or more, or tetra. 1-1.5 g./day, ? 4 weeks.	Str. may be combined with pen. Chl. also reported effective.
Anthrax	Pen. 0.5 mega b.d. for 5-7 days, or tetra. 1-1.5 g./day for 5-7 days.	Chl. also effective.
Gas gangrene	Pen. 1 mega t.d.s.	Surgical toilet of wound remains essential. Also give antitoxin.
Erysipeloid	Pen. 0.5 mega b.d.s.	
Weil's disease	Pen. 0.5 mega t.d.s., or tetra. 1-1.5 g./day.	Treatment often ineffective in severe cases.
Brucellosis	Tetra. 1-2 g./day for 2-4 weeks.	Addition of str. 1-2 g./day said to reduce relapse rate.
Tularæmia	Str. 1-2 g./day for 7 days, or tetra. 1-2 g./day for 7 days.	
Plague	Str. 2-3 g./day ? 5-7 days, or ? tetra. 2 g./day for 7 days.	Sulph. less effective but of value in prophylaxis. In severe cases also give antiserum if available.

Condition and Type	Drug, Dosage and Course	Remarks
Rickettsial infection		
(1) Scrub typhus	(1) Tetra. or chl. 6 g. in 24 hours, repeat if necessary.	Drugs only suppress disease; cure due to immunity after 2nd week.
(2) Other forms	(2) Tetra. 50 mg./kg./day, or chl. 50-100 mg./kg./day.	(2) In severe cases tetra. I/V 5-10 mg./kg./day at first; course of 4 or more days. Effect least striking in Q fever.
Virus		
(1) Psittacosis—L.G.V. group	(1) Tetra. 1-1.5 g./day, course varies, or chl. 2-3 g./day.	
(2) Others	(2) Ineffective, except in control of secondary infection.	
Venereal disease		
(1) Syphilis	(1) (*a*) Procaine pen. 0.6 mega/day for 10 days. (*b*) As above for 10-20 days (? bismuth in addition.)	All forms; treatment by expert advised. (1) In special circumstances benzathine pen. 1.2 mega, single dose.
(*a*) Early		
(*b*) Late		
(2) Gonorrhœa	(2) Procaine pen. 0.3 mega, one dose.	(2) Str., tetra., chl. and erythro. also effective. Many strains now resistant to sulph. In chronic case response often poor.
(3) Lymphogranuloma venereum	(3) Tetra. 1.5-2 g./day for 5 or more days, or sulph. 5 g./day for 10-14 days.	(3) Chl. also effective. Buboes may need aspiration. Pen and str. useless.
(4) Granuloma inguinale	(4) Str. 3-4 g./day for 5 days, or tetra. 1.5-2 g./day.	
(5) Chancroid	(5) Sulph. 5 g./day for 10-14 days.	(5) Str., tetra. and chl. also effective.
Other spirochætal infections e.g. yaws, pinta, bejel	Procaine pen. + 2% aluminium stearate 1.2 mega; repeat at 4-5 days, or benzathine pen. 1.2 mega, single dose.	

MEDICAL EDUCATION AND THE GENERAL PRACTITIONER*

By GEOFFREY O. BARBER, O.B.E., M.B., B.Chir.

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The story is told of Sir James Mackenzie that as a child of five years of age he set forth from a Scottish farm to go to school for the first time. The small lad was eager to go and so to make a beginning of his work in the world. But he has left it on record that when he returned home again, after the first day's work, he announced that his education was finished. He had had enough of it!

That child grew into the great man whose memory we are here to honour today. The subject of medical education was very dear to him, and he wrote a good deal about it in his later years. He lived in the days when every medical man was in general practice, and specialization and what is now known as a consultant status only developed through some special interest which was carried on alongside the ordinary wide application of medicine which we think of as general practice. In consequence, medical teaching was designed to produce a good view of general medicine, and to prepare a man for life as a general practitioner, out of which he could in turn develop a specialty according to his bent. Although Sir James Mackenzie's name calls to mind one of the greatest heart specialists who have ever lived, he was in general practice for twenty-eight years and he did in fact return to general practice at the end of his life.

It is since his time that the growth of scientific knowledge has increased to such an extent that, in order to specialize in one particular branch, a man must direct his main attention to it early in his career; and it is he who will in turn teach the students of the next generation. So that we are now in the position that the selection of medical students, and their subsequent teaching (up to qualification), are almost entirely in the hands of specialists. This has been generally recognized during the past twenty-five years, and there has been a number of attempts to revise the medical curriculum; and a great deal of thought and careful discussion has gone into these attempts. But today I want to do something fresh. It is difficult to look at the problem without any preconceived ideas, without thinking at once in terms of the methods of traditional medical education. All the same I would like to go right back to first principles and to think out just what it is that we are trying to do, and how best we can do it.

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*The second James Mackenzie lecture, delivered before the College of General Practitioners on November 19, 1955.

THE AIM OF MEDICAL EDUCATION

What sort of a young man do we want to produce when he qualifies? And since we are considering 'medical education and the general practitioner', let us think of him as probably going into general practice. We can say at once that his future branch of medicine should not be taken too much into account, and that we want to produce what is best termed a good basic doctor: that is to say a young man or woman who after registration can go on to build equally satisfactorily on to his training in order to become a general practitioner, a consultant, or a medical administrator. What sort of young man should this basic doctor be? What qualities should he possess, and in what order of priority should they be instilled?

He must of course have acquired a sound academic knowledge of the human body and mind in health and disease, with due regard to age and conditions of life—that I shall call simply professional skill. His outlook should be humanistic rather than materialistic—a patient should be a human individual rather than a collection of systems—that I shall call humanitarianism. And he should have some appreciation of the necessity for organization in the different branches of medical practice.

PROFESSIONAL SKILL

There may be some who would question my putting professional skill before humanitarianism. But I am of the firm opinion that I would rather be in the hands of a man with an accurate knowledge of medicine, and with but little of the milk of human kindness, than in the care of the kindest man imaginable who didn't really know his job! We must put first things first, and to be a good doctor one must have sound academic knowledge. Serious lack of the basic principles cannot be compensated in any way. Hence I believe that the general practitioner just as much as the future consultant must continue to be taught the various branches of medicine and surgery by specialists in those branches. But, and here I have a very big 'but', the student must be given a much broader view of disease than he can possibly get in hospital alone. The conditions which produce illness, and the first symptoms and signs of disease, are all to be observed *outside* the hospital. What is seen in the wards and outpatient departments is only a short section in the history of each patient's contact with medicine. The most important service that a doctor can do for his patient is to recognize illness at its very earliest possible stage, and it is these early stages which are conspicuously lacking in the material which is available for the teaching of students.

THE SCOPE OF MEDICINE

A great artist could find a magnificent subject if he were to look at mankind through the eye of a doctor. To do the subject justice would need a vast bas-relief, showing humanity through its various stages. First the pregnant

mother, then childbirth and infancy, childhood, adolescence, lusty manhood, courtship, marriage, the willing breadwinner, parenthood, the gradual effect of all life's stresses and strains, onwards to the realization of limited powers and the gradual decline into old age and finally death. If a family doctor lives long enough, he is able to observe most of these stages in the same individual, and collectively he may see every stage during the short space of even one day. But how much of this is seen in a teaching hospital? Some would argue that it doesn't matter—that general principles can be taught on the advanced and difficult case just as well as on the early or apparently trivial one. What *does* matter, however, is that from the start of his medical career every student should realize plainly that what he is being shown is in fact a short incident in a very much longer process, the beginnings of which he has not seen, and the end of which he will not see unless he goes out into general practice. And again he must be made to realize that there is a great difference between the behaviour of the living organism *in vitro*, and *in vivo*. The germ in the culture dish may behave quite differently from the germ in the living tissue, and in the same way the patient in the hospital bed is a very different creature from the same patient in his own home and family and job. The patient in hospital is rather like an animal in the zoo, living under conditions which are artificial and quite unlike his natural environment, whereas the general practitioner is in the position of the big game-hunter who studies his subject in his natural environment, his lair in the jungle, in fact the patient in his home.

That is the first important point that I want to make, namely, that disease is an affair which starts outside the hospital, which often ends outside the hospital, and which may never even come near the hospital. So that to get a true view of disease, the student *must* have an opportunity of studying the whole picture and not just a short slice of it.

HUMANITARIANISM OR SYMPATHY

Academic skill without humanitarianism is a barren thing. St. Paul said it all much better than I can in his Epistle to the Corinthians: 'Though I speak with the tongues of men and of angels, and have not'—charity? love? humanitarianism? love of one's fellow man? The Greek word is ἀγάπη and we have no satisfactory single word for it. How can we best define this quality? It was put into beautiful prose by an anonymous writer in the *Lancet* some years ago:

> 'Probably the one gift a general practitioner must have or acquire is being able to put himself in the patient's place—see with his eyes the sordid hopeless scene, hear with her ears the cry of the unborn, feel the longing behind the placid face, be in the factory where it happened, sense the closing walls of circumstance, glimpse the coloured toy that is the end of all desire, know the slow winding sheet of toxæmia, the hope that flickers in old age and death, and the fear that has no feared thing. In short, *sympathy*, a subject not in the curriculum'.

Yes perhaps sympathy is the best word, a sense of suffering along with someone else.

Dr. Ronald Gibson, the provost of the South-East England Faculty, has given another graphic picture of this attribute of the family doctor (*Lancet*, 1955, **ii**, 409):

> He was standing on a ferry waiting for the cars to embark, and he noticed a middle-aged man in a rather dated open two-seater with a B.M.A. badge on the front of the car and a half-closed sphygmomanometer thrown on the back seat. He says that nothing needed to tell him that he was just the type of man I am trying to describe, for he speaks of how an old lady leant on the car and started chatting. And from the way she spoke to him you could see that he wasn't just her doctor; he was her *family* doctor, an old friend and an honorary *ex officio* member of her family.

How then can we best sum up what is meant by humanitarianism? I think one can best define it as the sum of all those qualities, apart from professional skill, which one looks for in a good doctor whether he be a general practitioner or consultant: the qualities you look for when you are selecting the man to whom you yourself are going to entrust the health and happiness of your own wife and children.

ORGANIZING ABILITY

This is really the application of academic skill to a series of varying situations. It is necessary in every branch of medicine if a man's professional skill is to be used to the best advantage. But I do not think it is a subject which requires to be taught to the undergraduate. Its place is in post-graduate education, when a man is choosing the particular branch in which he is going to practise. In hospital the consultant has a large staff of trained personnel, but the general practitioner stands or falls by his own initiative.

In the Educational Number of the *British Medical Journal* a year or two past, I described the strangeness of sitting in my own consulting room for the first time, over twenty-five years ago. It seemed a dingy little room in the state my dear old predecessor had left it, papered in black with thin green stripes, with ivy climbing in at the window, and damp, mildew and dust everywhere on unopened samples and medical journals. There was no running water, and a dim naked gas jet for light. In the dispensary the bottles stood three deep, coated with dust and with labels which were strange even when I could decipher them. Pride of place was given to a large bowl of leeches (later one escaped, and my wife kept clear for weeks afterwards). I found that it was a hard job to apply my academic knowledge to a whole series of novel situations, and the majority of the ailments for which I was consulted were ones that I had not met in hospital, because they had never been serious enough to get there. There was the whole organization of a general practice, the technique of nursing a person in his or her own home, all the questions which involved cooperation with district nurses and re-

lieving officers, local health authorities; all these were things that I was meeting and hearing of for the first time.

But the very antiquity of the set-up gave an opportunity to start from scratch to build up a modern practice organization. Running water was the first innovation, for on my arrival the old doctor used eagerly to await my evening visit, and his first question was 'How many barrels today?' An odd question from the family doctor, but quite understandable when I say that the water to fill the medicine bottles came from an old cider barrel precariously wedged up near the ceiling. A greenish tinge in the liquid warned that it was running low, and a maid—a real maid, in black with a frilly white apron, cap and streamers—was summoned down the long passage to climb up a step-ladder and refill the barrel from a large polished brass jug. Three barrels meant that the young man was going down well!

So much for one's work in the consulting room. What about practice in the patients' homes? Conditions there were primitive too. Twenty-five years ago there was no electricity and only very limited gas; main water and main drains in a small radius; nine-tenths of the houses had none of these. Many a general practitioner knows what it means to conduct a difficult forceps case under these conditions, or to do a post-mortem examination in the depth of winter with the local village-well frozen. I remember one such occasion, one night when I was on my way to a New Year's Eve dance, dressed in 'tails'. My assistant was the village policeman, who was so well fortified with whisky that he upset one of the two buckets of water that the village had managed to provide, and nearly burnt the whole place down by upsetting the Tilley lamp, which had been specially borrowed from the local pub.

Even nowadays general practitioners have to contend with equally primitive conditions under which they must set about practising the up-to-date academic skill they have acquired in hospital, and it is neither fair nor sensible to launch them without some preparation for the enormous change in the technical application of medicine. But I want to make it clear that I have never thought that all this side of general practice should—or ever can—be taught to the student in hospital. I believe that those who are responsible for the education of future general practitioners should open the student's eyes to the need for this particular experience, and then see that he can get it.

I hope that my picture is emerging slowly, like a negative which, as a boy, one developed in a plate of developing mixture in a photographic room: the young doctor with a broad view of the present state of our knowledge as to how the body works and how it may break down and how to set about dealing with faulty functioning. This young man must have sympathy with his patients as individuals, he must have a knowledge of how much he can do himself, and what is the scope of the specialties which he can call to his aid when a particular case is beyond him and, finally,

how to organize this work so that it provides a good service for his patients, and a satisfactory professional life for himself and his family.

THE ROLE OF THE GENERAL PRACTITIONER

How are we going to produce him? Are *we* sufficiently conscious of our responsibility? By 'we' I mean the whole profession, and today let us apply that question particularly to ourselves who are gathered here, general practitioners of the present and passing generations. What can we contribute to this future generation who will take our place? What inheritance, good or bad, are we preparing to pass on to them?

The first thing we have to do is to take this responsibility seriously. There is surely no one of us who has not something to pass on to the students of the future, and as the demand grows (and it is evident that it is doing so already) for us to take students into our practices for a short glimpse of general practice during their clinical years, more and more of us must come forward to volunteer to take students. And when we take them, it must be with a very definite idea as to what we are trying to show them. Of course we are trying to give them a general sort of bird's eye view of the type of professional life we are living, but we ought to aim at impressing them with something considerably more than that. It is not a matter of picking out our interesting cases, which might be useful later on in an examination, although some students seem to have the idea that that is the interesting part, and that the common or garden stuff of the day's surgery is really a series of trivialities and certificates. It is just that impression that we have to correct, and I believe that we should say to each student when he first starts his week with us:

> 'In hospital you see cases of tuberculosis and of cancer which have come in for treatment, and those which have come early enough can be offered quite reasonable hopes of a cure. Now both these diseases begin insidiously; around us all the time there is a number of cases which are still at the stage of causing only a vague disquiet in the patient, which has not yet even taken them to the doctor. During these next few days a large number of patients will come into this consulting room with a whole variety of symptoms; it is my first duty, and yours so long as you are with me, not to let one patient who is suffering unconsciously from the early stages of serious diseases such as tuberculosis or cancer come into this room with whatever minor ache or pain he is already feeling, and go out again without our having put him on the road to an early diagnosis and proper treatment. So, however apparently trivial the complaint, one must never let a patient go until one has satisfactorily answered the question, "Can this be an early case of serious disease?" '

The second thing that we have to show these students is the great truth to which I have already referred, that throughout the life of every patient there is a continuous series of fluctuations in health, that each body inherits a different reaction to stress, that a particular disease is brought on by a number of quite different etiological factors; and that an accurate knowledge of the patient's heredity and environment is of an importance equal

to all the diagnostic and laboratory helps that we have to hand nowadays.

It is here that we should stress the question of our chronic patients. In hospital the student gets the idea that the natural sequence of events is consultation, diagnosis, treatment, *cure*. But a vast amount of the work of general practice consists in dealing with one-way processes in disease and degeneration, and we have to try to help people to live as best they can along with infirmities which we can only *alleviate*. So the student must see that this type of case—a chronic case—is really the highest test of good general practice, never to let these patients feel that nothing more can be done for them, always to give them encouragement and help. And, incidentally, to remember that it is these people who can draw on their long experience of doctors of every sort to tell their neighbours whether they think we are any good or not!

We can emphasize the importance of the mentality of the patient, the influence of mind over matter, or psychosomatic medicine. And the student may go back to hospital with a greater respect and interest for the psychiatrist and his influence on the patient's physical condition: he must learn to help the patient to 'bare his mind' as readily as he will 'bare his chest'. For instance there is often a fear of disease (especially of cancer), that underlies the trivial symptoms but which the patient dare not admit openly at first and will only confess to a sympathetic questioner.

During the short time that the student is with us, let us try to give him a good impression of the relationship between the general practitioner and the hospital. Take him into the local hospital to see our patients who are in there, and show him that it is our duty to follow their progress and to talk to the physicians and surgeons who are looking after them, so that their care is a continuous process. These young doctors must never get into the habit later on of sending their patients off to hospital and forgetting all about them until they reappear with a discharge note.

When I have been discussing this question of taking students into general practice, I have often been told two objections to the scheme: one is that the general practitioner has not time in an already overcrowded week to do this; the second is that patients would not like a young man coming round with him. I certainly do not believe that either is true or has been found to have any weight by people who have tried the scheme. In the first place we all find that we gain quite as much from these students as we can possibly hope to give to them. Personally I get considerable post-graduate teaching when I can tap the brain of an intelligent young man once one breaks down a certain barrier of diffidence or shyness, and it is quite fascinating and rather humiliating to find how out of date I sometimes am. It is great fun defending the old methods against the new, and at the same time the second objection is quickly overruled by the fact that the patients realize that here is someone with new ideas and a fresh interest in their case. In fact I have been slightly shattered by the comments one

or two patients have made on the satisfactory improvement in their condition since I adopted the advice of that clever young man I brought round with me last week!

There is another important point that I would like to make about taking students. It provides a wonderful opportunity for compulsory self-criticism. We all tend to get just a little bit slipshod both in our technical procedures and in our way of thinking, and in dealing with patients (which of us has not experienced that consciousness of failure when we have seen the slightly hurt look on the face of a patient who may have come quite a long way and plucked up quite a bit of courage to see us and yet, because he has arrived at an awkward and rushed moment, has had rather a hurried consultation and a slightly brusque dismissal?). A student may not always ask why we did something in a certain way, or why we left out something else, but it should be enough to make us continually on the watch not to give him an idea of slipshod medicine; and I have found myself making a mental note that I must pull my socks up in future, and not allow laziness or the confidence that may come with increasing years to detract from conscientious methods which were instilled into me during my hospital days.

There is yet one more thing that we should teach these visiting students. There are very few of us who, if we had all of our time over again, and had our present knowledge of the sort of life that we should lead as family doctors, would not choose to take the same path. I feel that we should let students know this, that what is called general practice can give that satisfaction in one's work which ranks only with a happy married life in the good things that we can find in this world.

WHAT THE STUDENT THINKS

It has been my good fortune to have to judge a number of students' essays on the best methods of teaching the student-patient relationship. There is a good deal of food for thought in what many of them say. One is reminded of oneself as a student. Probably to our teachers, we were 'good for nothing, lazy, drunken sort of fellows' as Sam Weller says; but there were times when we took life very seriously, particularly this future profession of ours. It was an impressionable age, and it is a humbling thought to remember what a deep influence some of our teachers unconsciously had over us, when we think that we ourselves may be exerting the same power over the students of the present day.

Certainly in their essays these students left one in no doubt as to their acute observation of their teachers, for each one is singled out either as an example to copy, because he is considerate, gentle and patient, and always appears to be dealing with the 'person' as opposed to the case—or he is studied as an example of bad manners, short temper, and general lack of sympathy. Particularly in his early clinical years, the student is still at the stage where he puts himself in the place of the patient, before experience

might possibly have hardened him to the sight of human suffering; and the moral is obvious: we must keep a most strict discipline upon ourselves, especially when a student is observing us. I know that a dull stupid patient can be infuriating when I am trying to get some sort of accuracy in his history. When his vague and evasive replies begin to sharpen my questions, I try to stop and think to myself 'the fault is not with the patient, but because his mentality is poor. This is a challenge to my ability to surmount the difficulty, and by cunning and patience to extract the patient's history in spite of himself'.

Another point made in these essays was a desire for some dogmatic teaching. The student is doubtful of his future ability to imbue confidence in his patient. So he likes the teaching of a man who appears sure of himself, particularly one who does not require every radiological and bacteriological negative finding before he feels he can safely give a diagnosis. There is, I know, a small tendency among patients nowadays to demand hospital investigations but some of this is only a phase of 'it's me rights, doctor'. Most of them prefer to be told that in their case no further investigation is necessary, and they respect the opinion of a general practitioner who can tell them so. In fact, the confidence of the patient can be embarrassingly complete, for I remember, a few days after starting practice, overhearing two patients comparing me with my predecessor. I came off badly, for as one old lady remarked to the other: 'this young doctor don't know so much, he has to *examine* you to find out what is wrong'.

Those who teach in hospitals should bear in mind that much of the unnecessary expense in x-ray film and pathological procedure is due to routine investigations by young housemen and registrars who have been taught such excessive caution that they arrive at the stage when they do not know which tests to leave out.

THE MEDICAL CURRICULUM

And so we arrive at a consideration of the medical curriculum. As it stands, is it likely to produce the basic doctor of whom we have been talking, and if we have to criticize it, can we produce constructive criticism so as to make suggestions for a better curriculum?

Let us deal first with the question of examinations. I agree wholeheartedly with Dr. Clark-Kennedy, the former dean of the London Hospital Medical School, when he wrote recently in the *Lancet* (1955, **ii**, 104):—

> 'I am an unrepentant believer in the examination system. I do not say that it is perfect. Indeed it is clearly far from that. But in my judgment, only the man who can rise to the occasion (in practical medicine you have to rise to a succession of occasions) and pass the right kind of examination, is fit to be let loose on the general public as a doctor. If he cannot do that, he would be well advised to contract out, before it is too late, and get started on some less dangerous profession'.

More attention should be paid to how a candidate sets about answering a

question, than to his actual knowledge of abstruse fact. I well remember in a final surgery examination, finding to my horror that my viva was to be conducted by the most dreaded of the examiners of that time. When my turn came, he presented me with a jar in which there was a very small piece of white tissue, about the size of a large postage stamp, with a neat round hole in the middle. It was not my inspired guesswork that he was after but, as Dr. Clark-Kennedy has said, to see how I rose to the occasion.

Regarding the content of the medical curriculum I would commend Professor Alexander Mair's article giving his survey of opinion among graduates from St. Andrew's University (*Brit. med. J.* 1955, **ii**, 526). It is a valuable factual piece of work, which gives a definite answer to what doctors in practice had to say about their preparation during their clinical days. And it agrees extremely well with the various surveys that have taken place in recent years on morbidity in general practice. Over twenty years ago, I took a thousand consecutive cases in my own practice and classified them according to the various systems which were mainly involved; the result was a great surprise both to myself, and to those teachers to whom I showed it, when we compared the incidence of the group of diseases with the time spent in the curriculum on that particular group. For instance, minor psychiatric disturbances, skin complaints, ear, nose and throat cases, and subclinical peptic ulceration all had a high incidence against a low teaching time.

Mental discipline is only achieved by methodical training. There is so much knowledge to be imparted nowadays, that there seems to be a strong case for teaching mental discipline on subjects which in themselves will be of value to the graduate later on. If this principle is accepted, then it is obvious that one is going to change the curriculum radically.

THE PRECLINICAL PERIOD

The preclinical subjects must be pruned right down and only included in so far as they give the student an idea of the function and the structures of the body and of those substances which affect it. It means also that function and structure must be taught at the same time, and preferably by the same person. Gone are the days when every doctor was expected to be able, even if he didn't do it, to perform any operation in the textbook of surgery. Is there a logical reason for the continuance of the system of teaching anatomy and physiology separately? It is traditional because our knowledge of exact structures is so much the older, and our predecessors were taught in detail what they could dissect and see, without knowing very much about what those organs did and how they worked. It is the natural evolution of knowledge, to see something before you can discover how it works. (Atomic physics is a notable exception, and a very special case.) But now that the development of physiology has brought our knowledge of function up to the level of our knowledge of structure, surely these sub-

jects should be taught together at the same time and by the same person. I believe that the preclinical teaching on the human body should be systematic, that is to say based on the systems, and that structure and function should be taught simultaneously. The dissection of the chest should be under the same professorial unit which teaches on the cardiovascular and respiratory systems, the abdomen should go with the digestive and genito-urinary systems. The nervous system should be taught as one, anatomy with physiology; and above all, the skeletal system, those dry bones of the anatomy lecture, should be clothed with flesh by the orthopædic surgeon; so that those dissections of muscles and tendons and their relations to nerves and arteries, take on some meaning to the bewildered student. This would lead in effect to the disappearance of the subject of pure anatomy as we all knew it and make it a postgraduate subject for the aspirant to the Fellowship.

Again, organic chemistry and biochemistry have all become so complicated, that it seems quite impossible to give the student a complete account of the chemist's present factual knowledge. What the student needs is an understanding of the principles behind the facts, a basic education on to which he can build later on if he wishes to specialize in that side of medicine.

THE CLINICAL PERIOD

When we come to the clinical period, I want to say with the very greatest of diffidence that the most important thing is to teach our teachers. I believe that when the time comes that every teaching consultant has had a glimpse of the scope of general practice, then there will be little need for this kind of discussion.

I am very fond of a story about Lord Horder. He was called down to see a patient by a young man who had recently left hospital and settled in the country. After the consultation was over he asked the young man how he was getting on, and was told that he enjoyed general practice, but that being singlehanded he rarely had an opportunity of taking his wife out for the evening. 'Well take her out this evening', said the old man, 'and let me stay and do your evening surgery. I would so enjoy it'.

Next I want to plead for a far greater integration of the various branches of medicine. Hospital wards tend to be divided strictly into medical and surgical, and yet every general practitioner knows how difficult it is when he speaks to the porter on the telephone to know whether to ask for the house surgeon or the house physician, because his patient might equally go to either (in fact he very often finds that whichever he decides to send his patient to, within the next few days the patient has been transferred to the other type of ward). But I did not realize this as a student; and I think it might be made plainer that they are not so completely apart. It would be most instructive if the surgeons regularly did a round in the medical wards, and vice versa; and it would give the student an opportunity of assessing the relative values of the two different outlooks on the same disease and on the same patient. Of course the really good teacher

will always manage to convey this interbalance of views by himself, but combined rounds would be a much better way of giving a student a basic training, and I am not at all sure that it is a good plan to examine an undergraduate separately in medicine and surgery. Would it not be better to give a combined paper so that it would be a test of his teaching to see into which category he himself fitted his attitude to the answer?

Again it does seem quite arbitrary to put the psychiatrist into a teaching department of his own in the hospital, for surely he ought to have at any rate a possible finger in the pie of these general medical or surgical cases. A brief and kindly psychiatric assessment of such patients could not fail to be of great help to physicians and surgeons alike; but I believe above all that what is missing in the teaching in a hospital is the patient's own family doctor himself. There are some hospitals where postgraduate courses for general practitioners consist of taking them on rounds along with students. This is admirable, for an intelligent chief will draw out of these general practitioners just that angle on his cases which his students need and which he himself cannot give.

This question of using the experience of general practitioners in the teaching of the students has been fully discussed by the Council of this College and, in our report on the Medical Curriculum to the General Medical Council last April, we recommended the introduction of a general practitioner into each medical school.

If a senior general practitioner were given a recognized position in a medical school he could see that all students are given a first-hand insight into general practice as part of their basic training. He could contribute to the teaching in the hospital along the lines I have just described, so that the student is conscious of the cooperation between the patient's general practitioner and the consultant. In no other way can he see how the one merges into the other, so that when his turn comes to practise medicine in either capacity he may fully realize the scope and limitations of each service.

There are other ways in which a general practitioner could help in a medical school. He could indicate trends in general practice, and could help in the selection of medical students. Certainly he could help those graduates who decide on general practice by ensuring that they can study the organization of good practices, by helping them to become established in general practice, and by advising in the planning of general-practitioner postgraduate courses.

CONCLUSION

Let me sum up very briefly. I have stated the case for a basic education of all undergraduates. This education should include a grounding in every branch of medicine and surgery, and it should therefore include that special integration of all the branches of medicine and surgery which we call general

practice. We should apply the same rules to general practice as we apply to any other branch of medicine. Every future doctor, whatever his line is going to be, must have a basic glimpse of general practice, the widest of all the applications of medical knowledge.

Later on, and after graduation, if a young man decides to be a general practitioner, then we should see to it that he gets an opportunity of learning the organization of general practice so that he may be able to lead a good professional life from the start without having to work out his own salvation. Apprenticeship in some form or another, either as a trainee assistant or as an ordinary assistant for a short time, or as a locum in a group practice, all offer a solution here, but it is through this College in particular that there is an opportunity for young men to benefit by pooled experience. That is what we are here for. This College has been founded to maintain and improve the standard of general practice, and how can we do it better than by starting the younger generation off with a wider concept of medicine than we ourselves achieved?

And so we come back to Sir James Mackenzie. It was his teaching that a proper understanding of health and disease could only be gained by observation of the fluctuations of function in an individual throughout the years. This idea of the continuous fluctuation of health and disease in the same individual should be introduced to the medical student during his undergraduate training, as a most important concept of medicine as a whole. And because the opportunity for study of this kind is not to be found in hospitals and consulting practice, here is a part of the undergraduate education which can and should be put into the hands of responsible general practitioners; it applies to the undergraduate whatever his future branch of medicine is going to be, for it will give him a truer concept of medicine as a whole and of his particular part in it.

Some people talk of this future as if it were something inevitable, predestined, and independent of their own wishes and ideals. How wrong! The future is in our hands. If we feel that we have an ideal of general practice, it is our duty to train the young men who will follow us, so that they will realize and live what we at present only dream.

GENERAL PRACTITIONERS' FORUM

OBSTETRIC RECORD CARD FOR USE IN GENERAL PRACTICE

By S. G. HAMILTON, M.B., B.Chir., D.C.H.

Thornton Heath

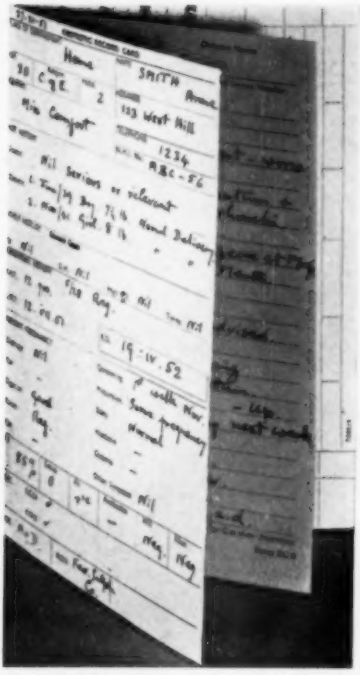


Fig. 1.—Obstetric card with N.H.S. Continuation Card inserted.

For many years I have felt the need for a maternity record card suitable for use in general practice.

Sometimes I have used an ordinary exercise book, and at other times I have made use of record cards such as are used in hospital clinics. The former may lead to failure to record all the essential information which may be required, or failure to record negative findings. The latter are usually too detailed for the requirements of a general practitioner, and are of an awkward size.

The folded card here reproduced is of stiff paper, $7\frac{1}{4}$ in. by $4\frac{3}{4}$ in., and can thus be inserted into the N.H.S. envelope. Furthermore, if extra space is needed an N.H.S. Continuation Card can be readily inserted with a piece of 'selotape' as a hinge (fig. 1).

The first page is designed for recording details required at the first interview (fig. 2).

The centre two pages record the examination and subsequent antenatal examinations (fig. 4).

The back page is for notes of the confinement and postnatal examinations, including examination and progress of the baby (fig. 3).

The layout is intended to show essential and important information easily.

OBSTETRIC RECORD CARD

PLACE OF CONFINEMENT

NAME

AGE | Religion | PARA

ADDRESS

MIDWIFE

TELEPHONE

N.H.S. No.

PAST HISTORY

General

Obstetric

FAMILY HISTORY

TB D.M. High B.P. Twins

MENSTRUAL HISTORY Normal Cycle

F.M.P.

L.M.P. E.D.

PRESENT PREGNANCY Quickening

Discharge Micturition

Pain Sleep

Digestion Headache

Bowels Oedema

Piles Other Symptoms

Blood	Group	Rh	Antibodies	WR	Khan

MISC. E.C.24

F.W.B

VITS | IRON

FIG. 2

CONFINEMENT Date

PUERPERIUM

INFANT Time of Birth Name

Sex Weight

Condition at birth

Examination

POST NATAL Date

General Condition Lochia

Complaints

O.E.

Abdo Breasts

Perineum Urine

Cervix B.P.

Uterus Hb.

INFANT Weight

Feeding

Examination

Remarks | Signature

FIG. 3

DATE

GENERAL EXAMINATION

Height	Weight	Breasts	Nipples
Deformities	Oedema	PELVIS	
C.V.S	V.V's	Uterus	
C.N.S	Skin	Cervix	
Resp. S.	X-R Chest	Pelvic Floor	
Alim.S.	Teeth	Perineum	
SPECIAL OBSERVATIONS		Pelvimetry	

ANTENATAL EXAMINATIONS

Date	Wk	Weight	B.P.	URINE Alb.	URINE Sugar	Fundus	Position	Foetal Heart	Sig.
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							
		Notes							

FIG. 4

FIG. 2.—First page of obstetric card, designed for recording details required at first interview.

FIG. 3.—Back page of obstetric card, for notes of confinement and postnatal examinations.

FIG. 4.—Centre two pages of obstetric card, for recording details of first examination and subsequent antenatal examinations.

DR. MESSENGER MONSEY (1695-1788)

AN EIGHTEENTH-CENTURY ECCENTRIC

By BRIAN HILL

Dr. Messenger Monsey (or Mounsey, for his name is spelled either way in contemporary references) is chiefly remembered today because he was the friend of the great Sir Robert Walpole, Garrick, Samuel Foote, Lord Chesterfield and other notable figures of eighteenth-century London. He is worth knowing, however, on his own account.

Dr. Messenger Monsey, 1695-1788

EARLY DAYS

Monsey was born, in 1695, of a good Norfolk family and used himself to say of his progenitors:

'The first of my ancestors of any note was a baker and dealer in hops, which two trades just enabled him with some difficulty to support a large family. Having a pressing occasion for a temporary sum, he robbed his feather beds of their contents, and supplied the deficiency with unsaleable hops. In a few years afterwards, a severe blight universally prevailing, hops became very scarce and enormously dear. His hoarded treasure was applied to: the contents were ripped out, and a good round sum was procured for them, though in a plentiful season they would not have been marketable. Thus our family *hopped* into the world from obscurity'.

Whatever the truth of this story, it appears that his father was in the Church and had been rector of Bawdeswell in Norfolk until he had been ejected from his living as a non-juror. Monsey's grandfather on his mother's side was also a clergyman. After his schooldays were over Monsey went up to Pembroke College, Cambridge, taking his B.A. in 1714. He then

studied medicine under Sir Benjamin Wrench, M.D., at Norwich, and became an extra-licentiate of the Royal College of Physicians in 1723.

On qualifying, he set up in practice in Bury St. Edmunds. There he might have lived and died an impecunious and quickly forgotten country doctor, tramping the Suffolk lanes in muddy boots or jogging along on a patient nag to visit his patients. Fate, however, threw a golden opportunity in the young doctor's way, for Lord Godolphin, the son of Queen Anne's Lord Treasurer and grandson of that formidable old lady, Sarah, Duchess of Marlborough, was suddenly stricken with illness while on the road to Newmarket. The nearest medical man happened to be Monsey. He was called in and so pleased his noble patient both by his skill as a doctor and by his unusual bedside manner and personality that Godolphin persuaded him to abandon his country practice and come up to London.

THE WHIGS' MEDICAL OFFICER

From that time Monsey's position was secure. To ensure a steady income for his protégé, his patron presented him with the post of physician to Chelsea College, later to be known as Chelsea Hospital. Under the terms of the appointment, however, Monsey was not required to live in, and consequently was able to set up his plate in the more fashionable quarter of St. James's. He soon numbered so many of the leading Whig politicians among his patients that he was regarded almost as chief medical officer to the Party. Sir Robert Walpole, himself, made use of his medical skill and became his friend. He was in the habit of playing billiards with his 'merry Norfolk doctor', of whom he inquired one day:

> 'How is it that nobody will beat me at billiards or contradict me but you, doctor?'
> 'Because', replied Monsey drily, 'they get *places;* I only get a dinner and praise'.

Blunt outspokenness of this kind, combined with an amusing, but biting wit and a real knowledge of literature, made Monsey many friends among the intelligentsia of the day. His tongue inevitably made enemies, too, and sometimes turned friends into foes. Dr. Johnson was one who never fell under the Norfolk doctor's spell. Boswell describes a scene where the lexicographer was 'vehement against old Dr. Mounsey of Chelsea College, as a fellow who swore and talked bawdy'. Garrick, too, although at first on friendly relations, eventually fell out with him when the doctor twitted him once too often with meanness. Indeed, Monsey composed some satirical verses on the subject wh ch began:

> 'Seven wise physicians lately met
> To save a wretched sinner;
> Come Tom, said Jack, pray let's be quick,
> Or I shall lose my dinner'.

Various remedies are suggested, including the then well-known Dr. Dover's powders:

'Some roared for rhubarb, jalap some,
And some cried out for Dover;
Let's give him something, each man said—
Why e'en let's give him—over'.

At length one of the medicos has a bright idea and jingles a few guineas under the patient's nose:

Soon as the fav'rite sound he heard
One faint effort he try'd.
He op'd his eyes, he stretched his hands,
He made one grasp—and dy'd'.

By a coincidence, Garrick did actually die just as this lampoon on him was about to be published and the author was persuaded to withdraw it. Another story illustrating Monsey's sharp tongue and uncompromising bluntness concerns a peer of his acquaintance who wrote to the doctor during an influenza epidemic, banning all visits between them:

'You see, my dear Monsey', he explained when they accidentally met one day, 'we are afraid of you just at this time, you come from so many sick rooms'.
'And you, my Lord', retorted Monsey, 'produce the very reverse effect on me, when I see you; you make me sick, but never afraid'.

A LETTER OF THANKS

Monsey was not, however, incapable of gallantry. Among his lady friends was Mrs. Montagu, the famous 'blue stocking', of whom he went so far as to say he did not believe a more perfect human being was ever created. In a letter to her dated 'March 4th, a minute past 12' he writes:

'Now dead men's ghosts are getting out of their graves, and there comes the ghost of a doctor in a white sheet to wait upon you. Your Tokay has got into my head and your love into my heart, and they both join to club their thanks for the pleasantest day I have spent these seven years. . . . I could have trusted till the morning to show my gratitude, but the Tokay would have evaporated, and then I might have had nothing to talk of, but an ache in my head and a pain in my heart'.

Among prettily expressed 'bread-and-butter' letters, this certainly takes a high place.

One of Monsey's peculiarities was to extract his own teeth, and those of his patients at times, in an unorthodox way. He tied one end of a length of strong catgut to the tooth and fixed a bullet to the other end. Then, charging his pistol, he fired and out flew the offending tooth. To a friend who tried to stop this rough and ready method of dentistry crying, 'I've changed my mind', the doctor is said to have retorted, 'but I haven't and you're a fool and a coward for your pains'; and he pressed the trigger without waiting for further expostulations.

AN ECCENTRIC WILL

On Lord Godolphin's death Monsey moved his quarters to Chelsea where he passed his last years in a retirement broken by constant squabbles with the functionaries of the Hospital. There, according to the 'Dictionary of

National Biography', he 'lived the life of a morose, but lettered hermit'. He died in the Hospital at the advanced age of ninety-four, leaving directions for his body to be dissected, after which 'it may be put into a hole or crammed into a box with holes and thrown into the Thames'. The first of these wishes was carried out by a surgeon-friend who is reported to have delivered a lecture on the body to the students of Guy's Hospital. Monsey's remains, however, were conventionally buried at Chelsea and a tablet to his memory was later erected in the church of Whitwell (now Hackford) in Norfolk, where he had inherited a small manor.

He left a comfortable fortune for his times, some £16,000. Most of it went to his only daughter for life and then by a complicated entail to her female descendants. His will contained some odd bequests as well. One young lady mentioned in it with the warmest regard was left nothing but a battered old snuff-box; another was first named as the recipient of a handsome legacy; this, however, was later revoked as the doctor said he had changed his mind on finding her 'a pert conceited ninny'.

Monsey was a free thinker in religious matters. Once when he was riding with an acquaintance in Hyde Park, the latter, deploring the corrupt morals of the age, broke off to say, 'but doctor, I talk with one who believes there is no God'. 'And I', snapped Monsey, 'with one who believes there are three'.

Here, written by himself, is an epitaph on this eccentric character:

> 'Here lie my bones; my vexation now ends;
> I have lived much too long for myself and my friends.
> As to churches and churchyards, which men may call holy,
> 'Tis a rank piece of priestcraft, and founded on folly.
> What the next world may be never troubled my pate;
> And be what it may, I beseech you, O fate,
> When the bodies of millions rise up in a riot,
> To let the old carcass of Monsey be quiet'.

(I am indebted to the Royal College of Physicians for permission to reproduce the portrait of Dr. Monsey.)

CURRENT THERAPEUTICS

XCVII.—PLASTICS IN SURGERY

By NORMAN C. LAKE, M.D., M.S., D.Sc., F.R.C.S.
Consulting Surgeon, Charing Cross Hospital

If the man in the street were to be asked what he meant when he spoke of a 'plastic' his thoughts would probably fly to his wife's imitation leather handbag, to his tobacco pouch or to other pliable articles which obviously displayed the property which in common parlance is called plasticity. But then he might remember that the electrical fittings in his house were said to be made of plastic and they certainly had no plasticity about them but were on the contrary brittle, whilst his 'plastic' comb and toothbrush had properties halfway between these extremes.

In this article no attempt is made to assess the surgical value of the various materials mentioned: critical discussion of the pros and cons of their use would be quite outside its scope. It is as well to record, however, that the popular commercial names applied to certain plastics do not imply standard chemical composition, for instance the terms 'nylon' and 'cellophane' are loosely applied to a number of somewhat similar substances with differences in chemical constitution which, whilst not much affecting their ordinary commercial use, may nevertheless be of importance to the success of their surgical application.

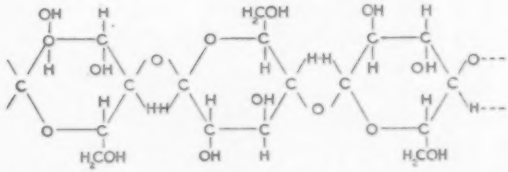
WHAT ARE PLASTICS?

It is indeed very difficult to give a comprehensive yet exclusive and precise definition of what a plastic really is. Perhaps the Greek origin of the word, 'something that can be moulded', will help, for at one time in its manufacture even the brittle electric fitting was truly plastic and was made by a moulding process. Such a definition is not entirely satisfactory, however, for obviously glass at certain temperatures is very plastic and easily moulded, yet it is not a 'plastic' in the common usage of that term. Nor does the addition of the adjective 'synthetic' get us out of the difficulty, for many plastics are made by modifications of naturally formed materials such as cellulose.

A common factor in the man-made plastics is the presence of carbon atoms; indeed, it is upon the unique structure of the quadrivalent carbon atom that the properties of the 'plastics' depend, silicon being the only other element remotely like it. The plastics therefore are organic materials and, as would be expected, many of them are found in living organisms: e.g. silk, cellulose; to a large extent the strength of tendons and ligaments arises from the plastic molecular structure of their individual fibrils.

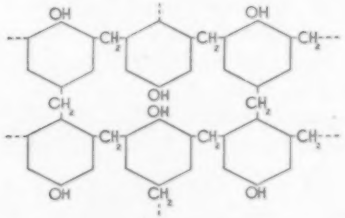
As is well known to every student of organic chemistry, the carbon atom is capable of joining up with itself to form long molecular chains, or some-

times rings, having various side elements or radicles attached. Thus, the cellulose molecule is known to be built up by the union of glucose molecules in this fashion:—



About 100 of these glucose units make up the cellulose molecule. The actual three-dimensional structure cannot, of course, be indicated on a flat surface. It will be seen that the cellulose molecule is a long one and, as the electronic linkages which hold the atoms together are almost incapable of disruption by ordinary physical forces, such a structure will have great strength in the longitudinal direction. The lateral forces (of Van der Waals) holding the cellulose molecules together to form fibrils, although much less strong, and capable of being reduced by heat and other means, are nevertheless considerable; it is ultimately upon these forces that the 'yield point' of a fibre depends when stretched.

It will be appreciated from the diagram that atomic linkages between the side chains are also possible, thus:—



Remembering that the structure represented is three-dimensional it will be realized that here the electronic linkages occur in all directions, giving a material which is rigid, such as 'bakelite'.

Various methods are employed to bring about the desired molecular structure: for instance, under such energizing influences as heat or ultra-violet rays certain simple molecules combine with one another to form chains, a process known as polymerization. Under certain conditions ethylene combines in this way to form polyethylene or 'polythene', thus:

$$(CH_2{=}CH_2)^n \rightarrow CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2 \text{ ------ } CH_2$$

THE USE OF PLASTICIZERS

The full development of desirable properties in many plastics, however, is only achieved by the use of 'plasticizers'. Most of these are solvents of the

plastic which, when used in small quantities, separate the plastic molecules and allow greater freedom of movement, i.e. they act rather like lubricants. The oldest of these is, of course, camphor, first used for this purpose in 1865 in the production of celluloid from nitrocellulose. A large number of different plasticizers is now used in industry; in some cases the monomer acts as plasticizer for the polymer. When a plasticized plastic is implanted in living tissue, however, the plasticizer may be released and prove to be noxious so that such plastics for internal use should be viewed with caution.

From the practical point of view plastics may be roughly divided into the thermoplastic and the thermo-setting. The former, usually long molecular chains without side links, can be softened repeatedly by the application of moderate heat and pressure without undergoing any change of structure, but the latter undergo changes which turn them into insoluble, infusible masses which cannot further be re-formed, i.e. the process is irreversible.

GENERAL USES IN THE OPERATING THEATRE

When a surgeon enters the operating theatre his first acquaintance with 'plastics' will probably be when he dons his 'mackintosh', for it will almost certainly be made of a thermoplastic material. His mask, if not constructed entirely of cellophane or perspex—fifteen years' experience has convinced me of the value and comfort of these (fig. 1)—will at least have a barrier of cellophane between its gauze coverings. His gloves too are plastic, although here it is at basis a natural rather than a synthetic product which is used. Similarly, the covering of the operating table and the tyres of the trolleys will be of plastic, this time loaded with conducting material to render them antistatic. In the conduct of the operation, depending upon its nature, plastics will be used to a great or less extent.

FIG. 1.—Face mask made of thin perspex, moulded to fit nose and cheek, thus preventing all 'misting' of spectacles.

NYLON

Monofilament nylon is now almost universally used for skin closure, replacing the natural plastic silkworm gut. The latter is monofilament silk obtained from the full silk gland of the worm just before the cocoon would be spun. Each strand thus represents the content of one gland and so its length is limited. Nylon resembles it closely, both physically and chemically, although it is stronger than the natural gut, can be sterilized by boiling, is impervious and, as it is produced by an extrusion process, its length is unlimited. Its extremely smooth surface facilitates insertion and removal

but has the disadvantage that knots slip the more readily. Braided nylon is also available—a thread woven from finely extruded nylon (i.e. like sewing silk)—and is used for buried sutures, although it has been known to cause excessive tissue reaction. In addition to being extruded as filaments nylon can be moulded in bulk into any desired form, such as sheets, tubes and artificial femoral heads. Sheets or films may be used for the preparation of face masks or as a dressing for wounds, tubes have been used experimentally to replace vascular excisions (see also 'polythene', p. 90), and, although most femoral heads have been constructed of acrylates, nylon heads appear to be particularly durable and resistant to frictional erosion. Unbreakable syringes, having both barrel and piston of nylon, are also available. In passing it may be mentioned that transparent plastic cranial inlays have been employed experimentally to study the cerebral circulation.

FIG. 2.—'Cock-up' wrist splint moulded from methyl-methacrylate.

THE ACRYLIC PLASTICS

The acrylic group of plastics, prepared by the polymerization of methyl-methacrylate, is used quite extensively in surgery. Externally they may be used in the preparation of splints (fig. 2) and spinal beds. As would be expected from their atomic constitution, they are translucent to x-rays, a feature of practical value when dealing with bone and joint diseases. Light in weight and comfortable to wear, they can be readily moulded when heated; furthermore they are unaffected by discharges.

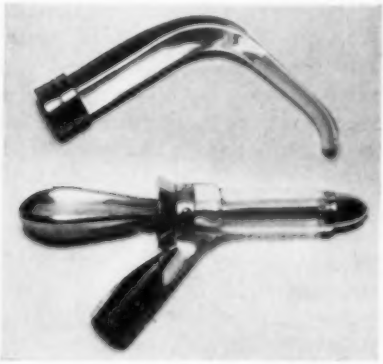


FIG. 3.—Retractor and endoscope made of perspex. In use, the source of illumination is attached to the proximal end of the instrument and the light is conducted along its whole length.

Many of the products of this group are quite transparent, e.g. perspex, so that lenses (instrumental and ophthalmic) can be prepared from them. The same property makes them valuable for the complete encasement of the smaller pathological specimens, whilst larger specimens may be contained within perspex jars, so reducing the risk of breakage and leaking. It is an

intriguing characteristic of these materials when extruded in rod or filament form that light, by multiple internal reflections, will travel along them no matter to what shape they are moulded. This is the basis of the 'coldlite' retractors and endoscopes (fig. 3) in which proximal illumination is used, the light, but no heat, being conducted along the instrument and escaping only where the smooth outer surface has been roughened.

A further recent development is seen in the experimental construction of flexible endoscopes in which a large number of fine filaments of the material are bound together, thus transferring from one end of the instrument to the other a kind of mosaic picture of any image thrown on to the receiving end. It is claimed that a picture can thus be transmitted even if the instrument be tied into a knot.

FIG. 4.—Acrylic head for femur, reinforced with stainless steel.

Another widespread use of the acrylics is in the making of dental plates and teeth. Here the strength, lightness, durability and resistance to corrosion of the material are particularly desirable. The chemical inertness of these products makes them acceptable for implantation in the tissues: acrylic plates moulded to shape may replace skull defects; hollow balls made of the acrylic 'lucite' have been used to obliterate the extensive cavity left after a pneumonectomy. Perhaps their best-known use is in reconstructive arthroplasty of the hip. The acrylic head (fig. 4), usually reinforced by a stainless steel stem, is inserted to replace the excised pathological head of the femur. As already mentioned, nylon heads are also used for this purpose.

'POLYTHENE'

Polymerized ethylene ('polythene') is another plastic which is finding increasing use in medicine. It is a tough pliable material which, if produced without the use of plasticizers, is well tolerated by living tissues, but care has to be taken with its sterilization. From the surgical point of view its most outstanding property is its resistance to wetting, which makes it especially valuable for intravascular work. Fine 'polythene' tubes (fig. 5) can be passed into and along blood vessels with little risk of clotting and so they are used for intravenous medication and for intra-arterial and intracardiac catheterization. These fine tubes will often remain in veins for some days without blocking. Larger tubes of the same material have been employed for the actual replacement of resected arteries, bile ducts and ureters; even the colon, the trachea and œsophagus have been thus reconstituted. A more

common use is for ordinary drainage purposes: the suprapubic insertion of a fine 'polythene' tube through a cannula into the bladder is a good method of dealing with an emergency retention of urine, but it can also be utilized for nephrostomy, ureterostomy and for the internal drainage of the cerebral ventricles. Indwelling 'polythene' tubes in the spinal theca for medication or anæsthesia add to a list already long enough to show that this is a versatile material the uses of which have by no means been exhausted.

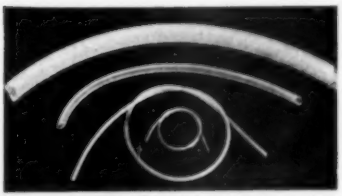


FIG. 5.—'Polythene' tubes of various sizes, the smallest being suitable for intravascular use.

CELLOPHANE AND CELLULOID

Cellophane.—Attention has already been drawn to the fact that the term 'cellophane' is applied to a number of materials which have a superficial resemblance to one another. The differences in their chemical constitution account for the discrepancies in the reports of their use in the body. Thus, in the early days cellophane was employed as a seemingly inert film to separate the brain from the skull and thus replace dura (a technique which was rapidly abandoned), whereas now it is employed for exactly the opposite purpose, namely, to stimulate fibrous tissue reaction. Large aneurysms are treated by wrapping them in a cellophane covering, whilst experimentally the kidney is similarly wrapped to produce hypertension. It can, of course, be safely utilized as a surface dressing for closed wounds.

Celluloid is another tissue irritant. It is perhaps of some historical interest to record that I saw it used in the radical cure of hernias when I was a student. As a further example of the fact that there is nothing new in the application of plastics to surgery it may be recalled that the use of collodion (closely allied to celluloid) as a sealed dressing for wounds dates back for many years. It is still employed, although some of the newer plastics are tending to replace it and are often used preoperatively as a sterile skin covering.

THE RUBBER-LIKE PLASTICS

From the rubber-like plastics prostheses can be prepared for use in exposed situations such as artificial ears and noses; here the slight translucency of the material gives the part a very natural aspect that could not be obtained in any other way. Some such plastics can be blown up to a sponge-like consistency and can then be used by surgeon and chiropodist to make any form of padding required. An interesting development has been the manufacture of artificial breasts for the post-mastectomy patient. Most of these are constructed of sponge rubber but in the United States a prosthesis has been devised consisting of a closed bag of semitranslucent rubber-like plastic shaped to the form of the breast including the axillary tail. It is incompletely filled with fluid, but without any air, before sealing. This not only recon-

stitutes the contour of the breast, including the anterior axillary fold, but also reproduces very closely the consistency and mobility of the natural breast.

THE PLASTIC CLOTHS

Into a different category fall the plastic cloths woven from extruded fibres. Nylon fabrics are, of course, universally known but the commercial material is not suitable for use in the body. Other cloths made of 'vinyon N' or of 'orlon' (a polymer of acrylonitrile) are well tolerated by the tissues. When suitably tailored and sewn to form tubes (fig. 6), they are used instead of grafts to replace excised arteries. There is no doubt that they are capable of doing this efficiently although it is too early to assess the long-term results.

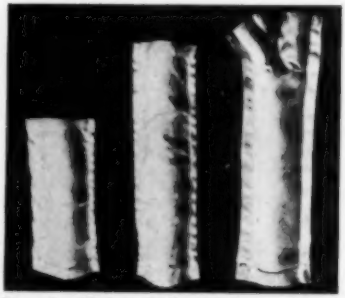


FIG. 6.—Tubes 'tailored' from 'orlon' cloth, suitably shaped to replace arterial resections.

THE THERMO-SETTING PLASTICS

All the plastics so far mentioned belong to the thermoplastic group; the thermo-setting plastics have little use in the tissues, but they are employed extensively in the manufacture of many surgical instruments and appliances. Thus, the insulation in most of our electrical machines depends upon such materials, either pure or in the form of laminated plastics. The latter consist of a basis of some fibrous material (e.g. wood fibre) which is bonded together with a plastic, usually under the influence of heat and pressure. Because of their great stability and insulating properties these materials may be used for the handles of diathermy electrodes, the insulating layers of endoscopes and so on.

CONCLUSION

Doubtless this list of plastics has many omissions but it will serve to show that the impact of plastics upon surgery has been a notable one. Whether we consider the humble plastic bowl which enables us to remove set plaster of Paris so easily or the 'orlon' tube to replace an excised portion of the aorta it has to be recognized that modern surgery owes a lot to the ingenuity and knowledge of the plastic chemists. 'Molecules made to measure' is their slogan and as properties and characteristics depend upon molecular form there is obviously great scope for the further development of materials to the benefit and service of surgery.

I am indebted to Miss P. M. Turnbull of the photographic department, Charing Cross Hospital, for the illustrations accompanying this article.

MY MOST INTERESTING CASE

XII.—'DEATH IN THE PARROT'S CAGE'

By A. P. THOMSON, *M.C.*, M.D., F.R.C.P.

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A LITTLE over twenty-seven years ago Dr. J. A. Knott, who had been my house physician, asked me to see a lady who was staying with her married sister in a large country house in Warwickshire and who had been seriously ill for several days. On the way to the house I asked Knott what he thought was wrong and he said 'I don't know, but the Widal is positive so I suppose it's an odd case of typhoid. If it is, it's the oddest one I've seen'.

The patient was delirious but could be roused to answer a few questions. She complained only of headache and a sense of severe illness; she did not refer to the troublesome and ineffective cough which gave her no rest. A few râles were found in the left upper lobe but otherwise physical examination revealed nothing of importance and, apart from the fact that her pulse was slow in relation to her continued fever, there was no clinical evidence of typhoid. The Widal, however, was strongly positive to paratyphoid B but there was no cross-agglutination to other organisms of the typhoid group. I commented on this but saw no reason to differ from the diagnosis suggested by the laboratory. Ten days later the temperature fell quickly and the patient was better but had developed a tense, tender swelling of the right parotid and I was asked to review the case. I aspirated some bloodstained fluid from this swelling for culture and after a consultation with Knott decided that for want of a better we must adhere to our original diagnosis.

'SHE LOOKED LIKE THE PARROT'

When I delivered this judgment to the family the patient's sister said 'I am very interested that you still think it's typhoid because my little girl says "Auntie's got what the parrot had" '. We then learned for the first time that a parrot had been bought some weeks previously. It had sickened and died and our patient had cared for it diligently to the end. I managed to see the little girl who had made the suggestion that Auntie had got what the parrot had, and asked her why she said so. With the simple and profound wisdom of children (she was about eight) she replied: 'Oh, Auntie fed the parrot and cleaned it, and when she got ill herself she looked like the parrot and sicked up all her food and coughed'. Somewhat chastened I had to admit that the child's reasons for her opinion were at least as valid as the evidence of an anomalous agglutination and I promised that I would look into the matter for I remembered reading somewhere about an epidemic of psittacosis—probably when I had to memorize books for the gratification of censors of the College of Physicians.

A study of the literature, particularly of the French reports of an epidemic illness in Paris in 1892-3 attributed to contact with sick parrots, satisfied me that the little girl was right, and I was confirmed in this opinion when the cultures from the fluid I had aspirated from the parotid gland yielded a bacillus very similar to that recovered by Nocard, in 1893, from the bone marrow of a parrot that died in Paris and had been the presumed source of infection of a human case. In British records I could find only a short note of two cases published by the late Professor G. L. Gulland of Edinburgh in 1924.

THE PARROT IN THE NURSING HOME

Despite diligent inquiries during the next six months I had no luck and heard of no similar occurrence. I then decided to publish a short note of the Warwickshire case and, in March 1929, was checking some references in the library of the Medical Institute when my friend and surgical colleague, H. H. Sampson, came in and asked me what I was doing. I told him and said 'I suppose you don't know anything about infection contracted from parrots'. He replied 'No, but I'll tell you where some people died of it a few months ago and that's next door to you'. Sampson and I at that time had consulting rooms in a house in the middle of Birmingham and next door to us was a large private nursing home. In November 1928 (four months after my consultation in the Warwickshire case), the proprietress of this home bought a parrot and trained it to sit on her shoulder while she visited patients. Sampson happened to meet her as she left a room, noticed that the bird looked sick and insisted that it should have no contact with any of his patients although a veterinary surgeon had seen the bird and had assured its owner that there was no risk of any infection to a human being. Within a few days the bird was dead. Shortly afterwards the proprietress developed bronchitis followed by broncho-pneumonia of which she died. Her personal maid who had shared in the care of the parrot had a similar illness which also proved fatal, and a third member of the staff had a slighter illness of the same sort from which she eventually recovered. The second of this group of three cases was admitted to the City Hospital for infectious diseases, and Dr. E. H. R. Harries, who had charge of her, kept careful notes of her condition. A comparison of these notes with the description of the French cases to which I referred him left little doubt in his mind, and none in mine, that the illness was in truth psittacosis.

THE SEQUEL

A short account of these cases, with a historical note, was published in the *Lancet* of July 20, 1929. It included a comment on the shocking conditions of the import trade in parrots which I had examined and also a criticism of the accepted veterinary teaching that 'no evidence had been disclosed to prove that [human cases] . . . suspected of being psittacosis did originate from sick parrots'. Presumably this extract from a recent standard textbook

had been responsible for the veterinary surgeon's mistaken reassurance of the unfortunate owner of the nursing home. One of the London newspapers used the *Lancet* article for a paragraph with a scare headline about death in the parrot's cage and within a few days I was summoned to the north of England to see a group of three more cases of psittacosis, one of which had given a positive agglutination to *Salm. typhi*. The diagnosis had been made by the wife of this patient who confronted her doctor with the London newspaper and the copy of the *Lancet* she had bought. Her acid comment 'Do you still think it's typhoid?' was perhaps excusable because she had all the time insisted, like the little girl in Warwickshire, that her husband had what the parrot had died of. Fortunately he recovered.

Within a short time reports of similar cases were published from all parts of the country and several doctors were good enough to send me notes of obscure illness in patients who had cared for sick parrots. It was evident that a considerable epidemic existed and I invited a member of the staff of the Ministry of Health to come to Birmingham to see three cases with me and to discuss restrictions on the import trade in the birds, for it was clear that most human cases were occurring after contact with freshly imported parrots and budgerigars. The representative of the Ministry was interested but not convinced that action was justified. When an influential local politician in Birmingham fell a victim to the disease a little later, however, the official view changed with remarkable speed. A question was asked in the House of Commons, the Ministry thought again and the importation of parrots and budgerigars was forbidden.

Restrictions on the trade in pigeons were also imposed, for evidence had accumulated to show that they might be infected. This indirect attack on pigeon racing involved me in some curious and inconclusive interviews with leaders of the sport. They were, for the most part, stout and solemn gentlemen from the north of England who made an odd contrast with the beautiful and beloved birds of which they could believe no ill. Their attitude to the whole affair was like that of the jury called by H.M. Coroner for the City of Birmingham as a matter of public interest, to review the circumstances leading to a man's death from psittacosis. After hearing much expert evidence and testimony about the trade in pet birds they returned a verdict that 'death was due to psittacosis but the parrot was not to blame'.

Early in 1930 there was a discussion on psittacosis at the Royal Society of Medicine. By that time the clinical picture had been more accurately defined: it was that of a typhoid infection but only rarely was the spleen palpable or were rose spots to be found. Signs in the lungs varied from scattered bronchitis to dense consolidation which suggested the presence of a pleural effusion. Of paramount importance was the history of contact with a sick bird, for only one case was mentioned which suggested infection from nursing a human patient. At this meeting I was able to present the necropsy findings of the late Professor Haswell Wilson in one of our patients who had had signs of massive consolidation of the lungs.

The affected lung substance was a dusky red colour and of a dry and almost crumbling consistence. There was no evidence of suppuration and the appearance was quite unlike that of ordinary lobar or broncho-pneumonia. Histological examination showed uniform consolidation: the exudate was fibrinous; cells were scanty and almost entirely mononuclear. There was no selective perivascular or peribronchial distribution of exudate as occurs often in influenzal pneumonia. Many of the smaller bronchi were filled with desquamated epithelium.

About the etiology there was still some doubt. In Birmingham, despite intensive effort, we had found an organism like that described in Paris by Nocard in no more than two cases (the first Warwickshire one and later from the scrapings of a parrot's cage). In London there was no instance of bacterial infection, but at this same meeting Bedson gave his preliminary report on the recovery of a filterable virus from a parrot which had been the cause of two human cases and was successfully passed on to budgerigars. His work ultimately solved the question of the etiology of the disease. Not only did he prove that it was due to a virus but he showed that the serum of patients gave a positive and distinctive agglutination to it. Diagnosis was thereafter placed on a sure foundation and it became possible to recognize slighter cases of infection that would otherwise have escaped notice.

The riddle of psittacosis is now the general problem of epidemiology. Why is it that in natural conditions epidemics wax and wane over long periods of time? A few sporadic cases still occur in this country and no doubt there is a risk of a widespread outbreak in future for reasons of which we have little accurate knowledge. Fortunately there is good reason to believe that the next epidemic will be readily curtailed by antibiotics.

CONCLUSION

In retrospect my first case of psittacosis is interesting to me for many reasons. First because the diagnosis was suggested by a young child who, quite untrammelled by the fetters of formal instruction, immediately recognized the points of similarity between the illness of her aunt and that of the parrot. Next because of the extraordinary good fortune of my chance encounter with Mr. Sampson in the library. My interest in psittacosis was flagging and had he not told me of the strange cases of illness which occurred in the nursing home next door to my consulting rooms, I might well have given up the search for more material. Candour compels the remark that in life we are often at the mercy of the contingent though we rarely admit it and attribute any small success to innate virtue rather than to chance.

The prolonged, accurate but abortive studies of the bacteriology of our cases by the late Dr. W. T. Hillier proved to me that in any serious and prolonged illness, secondary infection occurs with a frequency that I had not previously suspected and the discovery of it may lead a clinician into errors of diagnosis. After this experience I made bacteriological studies of patients gravely ill from diverse causes such as malignant growth, nephritis and tuberculosis, and found that in the terminal stages secondary infection of the blood stream by such organisms as *B. fæcalis alkaligenes*, *Staphylococcus aureus* and *Streptococcus viridans* was relatively common.

Finally I would say this: domesticated animals are an important element in human ecology. The recognition by Jenner of cowpox in the dairy maid as a protection against smallpox is the classical instance of the clinical importance of the broad view of human environment, and there are many other examples—bubonic plague, trypanosomiasis, tularæmia and the occupational diseases for instance. This field is not yet fully explored and contemporary interest in narrow, specialized techniques—valuable though they are—tends to obscure its potential fertility. The risks of wide horizons in clinical medicine are loose thinking and wild hypothesis uncontrolled by the discipline of repeatable experiment and statistical method. The lesson of the work on psittacosis from 1928 to 1930 and afterwards was that the rather crude definition of clinical experience led to the beautiful work of S. P. Bedson and an addition to established human knowledge.

REVISION CORNER

THE TREATMENT OF POSTMATURITY IN DOMICILIARY PRACTICE

THE subject of postmaturity is both topical and teasing. Topical, because with the drop in the maternal mortality rate more attention is being paid to the 'sleeping partner' in pregnancy—the baby—and also because the modern attitude to the family is one which expects a smaller number of children to be born and all of them to be healthy and survive. Teasing, because the evidence in regard to the condition and its results is conflicting. The difficulties which arise are those of definition; of agreement as to the consequences of postmaturity; of its recognition clinically; and of its solution in practice. The aim here will be to present briefly the evidence obtained within recent years and to discuss the use to be made of it within the framework of domiciliary practice.

DEFINITION

We think and speak loosely of 'maturity', 'term', 'postmaturity', with the general idea that the normal length of pregnancy is within a few days of the ten lunar months mentioned in the Wisdom of Solomon. Although there is a generally agreed standard of prematurity, though not a completely satisfactory one, it has been more difficult to achieve a standard of postmaturity. According to Penrose (1950), the mean duration of pregnancy as measured from the last normal menstrual period is just short of 280 days, with a standard deviation of 17 days. It would seem reasonable therefore to regard prolongation of pregnancy to within this time as being 'overdue', whilst after this time there could possibly be true postmaturity. But even then one can only say 'may be' because the data are derived only inferentially from the menstrual time and not from the true time of conception which of course is usually not known. Stewart (1952) studied the duration of preg-

nancy in 135 women whose pregnancy was dated by means of temperature estimations showing the ovulation time and hence the approximate time of conception. He found that the average duration of pregnancy dated thus was 266 to 270 days, but in fact even under these more accurate conditions it ranged from between 250 to 285 days, and some of his patients dated in the ordinary way from simple menstrual data would have had pregnancies judged to be even up to 349 days. It behoves us therefore to be careful in assessing evidence obtained in pregnancies dated in the ordinary manner, and also in the use of the word 'postmature' in the presence of the mother who may be disturbed to hear it.

THE POSSIBLE EFFECTS OF POSTMATURITY ON THE BABY

Simple clinical evidence obtained from the stillbirth rates in studied series of births has yielded conflicting material. Table 1 shows the results of recent investigations by various authorities. There is of course the fundamental difficulty of comparison in such statistics. The evidence, although conflicting, does seem to point to a higher mortality rate in the baby with prolongation of the pregnancy. The point then arises whether the risk to the baby is from the placenta ageing and becoming less efficient, or from hazards of birth from disproportion and difficult labour. The latter view

Authority	No. of cases	Criteria	Stillbirth rate
Clayton (1941)	455	14 days or more	6.15%
McKiddie (1949)	1,642	7 to 15 days 15 to 21 days 22 to 28 days	1.6% 3.3% 7.4%
Latto (1951)	171	14 days or more	2.8%
Hill (1952)	115	16 days or more	1.74%
Racker *et al.* (1953)	261 149	7 to 13 days 14 days or more	2.31% 8.72%
Daichman and Gold (1954)	123	14 days or more	2.4%

Table 1.—Selected published series of cases of postmaturity.

has been held notably by Clayton (1941), who has recently had support from the researches of Walker (1954), showing that as pregnancy is prolonged there is less oxygenation of the fœtal blood and thus the baby is working at an increasing disadvantage, particularly when labour starts.

The evidence therefore raises two questions. Are we justified in regarding postmaturity as dangerous enough to the baby to indicate induction automatically? Or, if we believe the danger to the baby mainly to arise in certain circumstances, do we feel that our management should depend upon selection and judgment? Finally, there is one other disturbing piece of evidence. Bickenbach (1947) showed that neonatal mortality, too, may be adversely influenced by the prolongation of pregnancy. In the future there-

fore evidence will have to be forthcoming in regard to the total mortality risk to the baby, not merely the risk of stillbirth.

THE CLINICAL RECOGNITION OF POSTMATURITY

Any practising obstetrician knows how difficult it can be accurately to assess the size, weight, and consistency of the baby *in utero*. The points made by Wrigley (1946) are important if they can be recognized: the bigger baby, the feeling of greater muscle tone, and the diminution in the amount of liquor relative to the baby as pregnancy is prolonged. One would hope here for more help from the radiologist than is customarily obtainable.

OBSTETRIC MANAGEMENT IN DOMICILIARY PRACTICE

From what has been said it is obvious that there are some grounds for uneasiness if pregnancy is unduly prolonged. The very fundamental principle of treatment is raised as to what interference is justified in the apparent interest of the baby alone. Is the evidence good enough to indicate the more or less routine induction of labour a few days past 'term'? There used to be an old country saying that a pear should be picked ten days before it is ripe, but ripeness is all and how are we to judge it accurately?

If only we had reliable signs or tests of maturity and an absolutely safe and infallible method of inducing labour, prolongation of pregnancy would cease to be a problem. Admittedly, some obstetricians practise routine induction of labour, at any rate in primigravidæ who go 7 to 10 days overdue, and they are satisfied that this procedure results in a lower risk rate to the baby and an easier labour for the mother. If this is done, however, many unnecessary inductions must surely be performed and any act of commission must itself have its own possible complications. Any of us who practise obstetrics are aware of these in induction although they do not always find their way into the reports of cases. The policy of routine induction can scarcely be the solution to be adopted in domiciliary practice. Here surely the approach must be to the individual appraisal of the case.

If pregnancy is prolonged the opportunity should be taken for a full and careful review of the case, and upon this review decision should be made as to whether to leave well alone, to induce labour, or to transfer to hospital care. A scrupulous history of menstruation and the progress of events in the pregnancy should be taken. The menstruation interval may be longer than the 'norm' of 28 days, with effect on the ovulation time. It may be possible to have information of the conception time. The clinical rate of progress of the pregnancy as assessed by the uterine size estimated at antenatal examinations may help. It is notoriously difficult to estimate with accuracy the size of the baby *in utero*, but great care should be taken to try and recognize a large baby or one showing any signs of disproportion. A history of previous labour will be helpful if the woman is a multigravida. The size of the pelvis must be assessed clinically and by x-ray pelvimetry if the patient is primigravid.

If, following this review, the baby is regarded to be fitting well in relation to the pelvis, the lie is favourable, and everything else seems normal, there would be every indication for awaiting the onset of labour normally. The presence of a big baby, a history of previous stillbirth, an occipito-posterior presentation or a malpresentation, hypertension, or the fact that the mother is an older primigravida or has had considerable difficulty in conceiving, would be indication for at least seeking a second opinion and most probably suggesting that delivery should take place in hospital. The real indication for induction of labour in these cases is the growth of the baby to such an extent as to make disproportion likely. Simple medical induction, with the omission of oxytocics, may then be followed by the use of surgical induction if necessary.

Whilst it is unlikely that the baby will die *in utero* before the onset of labour if pregnancy is prolonged, death of the baby during the progress of labour is certainly more common. For this reason, there should be careful observation of the course of labour, of the response of the fœtal heart rate to the uterine contractions, and of any evidence of fœtal distress. If there are signs of an unfavourable course in the first stage of labour the possibility of Cæsarean section would mean transferring the patient to hospital. If fœtal distress occurs in the second stage of labour a forceps delivery is indicated or at least the relief of perineal tension by episiotomy if the head is low. As the baby is working at an increasing disadvantage in regard to oxygen supply any general anæsthesia given to the mother should be accompanied by a free supply of oxygen.

CONCLUSIONS

The question of postmaturity is at present a perplexing one and the evidence of its occurrence and effects is conflicting. In these circumstances, in domiciliary practice it is best to remember that 'overdue' is much more common than true postmaturity. The aim of the practitioner should be to treat individually, and particularly to select cases which appear to be of poor omen rather than to adopt a routine policy of interference.

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THE PAINFUL HEEL

As a rule this condition interests the patient a good deal more than his practitioner. There may be no physical signs with which to make a diagnosis and moreover the patient usually expects to be cured. There is only a limited number of causes of painful heel, but unfortunately, in the past, a number of incorrect notions about the syndrome became current and this legacy still has to be lived down. The idea that the so-called spur, visible on the lateral x-ray, on the underside of the os calcis was a cause of pain and hence, by inference, should be removed, was a heresy that has crippled a lot of patients and is only recently dead.

Gout, rheumatism and gonorrhœa have all been blamed from time to time and the appropriate remedies prescribed. Since, in general terms, the painful heel tends to get better, almost any measure can gain a spurious reputation for success. When a patient presents himself with a painful heel the practitioner should give, at least, a cursory glance at the skin to note if, by chance, there is a verruca present or evidence of a recent puncture.

It is convenient to classify this syndrome into two groups: (i) those in which pain is complained of at the back of the heel; (ii) those in which pain is felt underneath the heel.

PAIN AT THE BACK OF THE HEEL

Apophysitis of the os calcis.—The patient, a boy or girl between the ages of eight and fourteen, complains of pain on the point of the heel. This is sometimes rather severe, though usually it is not much more than a nuisance when playing games or walking on pavements. On inspection there is no abnormality but on palpation marked tenderness is complained of along the postero-inferior edge of the bone extending forwards for a short way. Consulting-room function is normal; that is to say the child can prance about on her toes without pain. It is a clinical diagnosis and never in doubt. The pain is the product of a juvenile osteochondritis of the apophysis at the back of the calcaneum comparable with the better known Schlatter syndrome of the tibial tubercle. An x-ray is of no help but may be used to stop a fussy parent talking.

There can be no specific treatment; only symptomatic. The condition becomes symptomless in a few months and in the meantime some care-taking measure, such as tinkering with the heel of the shoe or discouraging games, or rubbing on a liniment, will fill in time until nature calls off the symptoms. Specialist advice, hospital consultations, and physiotherapy are all equally unnecessary and valueless.

Tendo achillis bursitis.—In this condition, pain and tenderness are located at the postero-superior angle of the os calcis. Its incidence is confined to young adults, usually women who have recently taken up nursing or some regimented occupation. Os calcis bursitis cannot occur in shoeless communities because it is the product of shoe pressure against a more than usually prominent postero-lateral tubercle. There may or not be an asso-

ciated enlargement of the bursa between the tendo achillis and the superior angle of the calcaneum. The presence of a bursitis is indicated by a soft swelling. The patient may have a good deal of pain, however, without bursal enlargement.

Simple means such as changes of shoes or removal of the stiffening from the back of the heel may make the patient sufficiently comfortable. A pad in the shoe which lifts the os calcis may also be helpful, especially if a bursitis is present. If these simple remedies are insufficient surgery may be necessary. The postero-superior angle of the os calcis is chipped off. This procedure always succeeds in relieving the symptoms but it is to be avoided until conservative measures have been proved a failure. The convalescence is not as short as might be supposed.

PAIN BENEATH THE HEEL

If an adult stands for an unusually long time the heels are apt to ache and become tender on palpation. The cause and remedy are equally obvious.

Plantar fasciitis.—This entity is the most baffling of the group and its imputed pathology has caused a good deal of confusion. The condition is a familiar one. The patient, a heavily built male of middle age, complains of a painful heel on standing and walking. The onset is insidious. On examination the tender spot is approached from the medial aspect and is found two inches anterior to the point of the heel and on the postero-medial margin. The tender spot is the size of a florin and is not situated at a point in firm contact with the ground. A lateral x-ray often shows the appearance of ossification of the attachment of the plantar fascia. Hence the term 'spur under the os calcis'. It is only fair to state that this x-ray appearance is often present in feet which are symptomless. The pathology of this condition is comparable with that of tennis elbow. It represents what is presumably a degenerative metamorphosis of the collagen fibres of a muscle origin into adult fibrous tissue. The cycle takes time to evolve, sometimes up to eighteen months; its completion is inevitable once it has started and the etiology is unknown. Clinically, as with tennis elbow, during the evolutionary phase the muscle origin is tender on pressure and painful under tension. The syndrome is self-limiting and treatment is only called for if the symptom of pain becomes troublesome. Clearly there is no specific treatment.

An attempt to relieve the pain on standing by inserting a sponge pad in the shoe is doomed to fail. However soft the pad the patient's weight is unaltered. Some relief is possible if the heel is raised because this, by inducing a cavus position of the foot, relaxes the plantar structures and reduces tension. Another method of relaxing the fascia is by applying a pad of sponge or felt under the instep anterior to the normal site. The heel is partially relieved from weight bearing and a cavus posture of the foot is induced. Generally the use of this kind of pad will keep the patient sufficiently comfortable until his spontaneous cure is complete.

Activist practitioners are often tempted to inject hydrocortisone into the tender spot, and sometimes they succumb. It is an empirical treatment which occasionally cures dramatically and sometimes produces an awkward exacerbation of pain for two or three days, often followed by real improvement. It is a capricious and hazardous procedure and practitioners who have spent their lives watching therapeutic comets flash across the sky only to fizzle out, may well be dubious and advise a less dramatic treatment by padding multiplied by time. The thought of surgery for plantar fasciitis must be instantly suppressed with a guilty blush.

The painful heel after recumbency.—This irritating member of the painful heel family occurs when a patient is beginning to get about after a prolonged spell in bed. It is more likely to occur if the patient shuffles about in slippers. The pain is in the heel and is severe enough at times to delay convalescence. Although the pain may be quite severe, rapid improvement is the rule and this is probably accelerated if the patient wears walking shoes. No special restriction is necessary. Physiotherapy may be of some help and is usually prescribed, if only to encourage the patient.

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NOTES AND QUERIES

Antacids in Peptic Ulcer

QUERY.—I find considerable divergence of opinion as to the efficacy of antacids in the treatment of peptic ulcer. Could you clarify the issue for me? I should also be grateful for advice concerning the use of orange and lemon squash by such patients. These drinks are acid and would therefore appear to be contraindicated in patients with peptic ulcer.

REPLY.—It is generally agreed that the presence of free acid in the stomach deters healing of gastric and duodenal ulcer and that the effect of HCl on the ulcer is to produce the pain. Conversely, if the acid can be neutralized the pain disappears rapidly and healing is encouraged. The taking of intermittent doses of antacid has been unsatisfactory because, especially in the case of a duodenal ulcer, the stomach usually empties rapidly and thus ejects the antacid and the acid output is high throughout the twenty-four hours. This has led to the development of tablets which can be sucked slowly between meals so that with every swallowing of saliva antacid is carried down with it. This has been shown to produce adequate neutralization. The difficulty at night is still formidable because sucking clearly cannot be carried out during sleep. To overcome this, substances like atropine and more modern preparations which slow the emptying rate of the stomach are given at night with a large dose of antacid, e.g. aluminium hydroxide gel, in the hope that its action will be prolonged.

The organic acids in citrous fruit drinks are weak and quite unimportant in respect of peptic ulcer.

A. H. DOUTHWAITE, M.D., F.R.C.P.

Antibiotics in Whooping-Cough

QUERY.—In your issue for October 1955, an article on 'The Hacking Cough' (p. 510) advised antibiotic treatment in whooping-cough. What is the antibiotic treatment of choice in whooping-cough?

REPLY.—It is most important to stress that chemotherapeutic substances are effective only in the earliest stages of whooping-cough, and are probably only effective before the twelfth day. *Hæmophilus pertussis* is a gram-negative bacillus and is sensitive to oxytetracycline, chlortetracycline and streptomycin. It is also sensitive to chloramphenicol, but it is in treating small children with this drug that most of the cases of aplastic anæmia and agranulocytosis

caused by it have been reported. Oxytetracycline in a daily dosage of 50 mg. per kg. of body weight, given in four doses six-hourly, for ten days, is the antibiotic treatment of choice.

Rudder and Vettermann compared the results of treatment in 318 infants during the period 1937 to 1947 without antibiotics, with a similarly affected group of 383 infants treated with chlortetracycline between 1947 and 1952. In the group receiving chemotherapy, the average stay in hospital was between four and five weeks, compared with eleven weeks in the group not so treated. Of those receiving no chemotherapy, 23.6% developed pneumonia, and 42% of these died, whereas 4.8% of those receiving chlortetracycline developed pneumonia, of whom 13% died.

It cannot be too strongly emphasized, however, that prevention is better than cure, and that immunization against whooping-cough is most effective.

KENNETH PERRY, M.D., F.R.C.P.

Treatment of Stevens-Johnson Syndrome

QUERY.—I should be gratetul for advice on the treatment of a case of Stevens-Johnson syndrome.

The patient, previously healthy, aged 37, first developed the condition in March 1954. He is a tiler by trade. The first symptoms were stomal ulcers and circum-oral and aural blisters. These gradually developed and did not improve with conservative treatment. After three days, a dusky macular rash developed over the trunk and limbs, the macules coalescing and causing intense irritation. Pyrexia developed five days from the onset, probably due to the severe oral sepsis. It was associated with a mild conjunctivitis but no urethral discharge. With the onset of pyrexia he was given intramuscular penicillin and the whole condition abated in the following five days. Local applications of calamine and phenol and lead and opium were tried but the most relief was obtained by sodium bicarbonate compresses. The second attack developed suddenly about three months later and he was immediately admitted to hospital, where the only abnormal finding was a raised E.S.R. He was treated with intramuscular penicillin, 'gantrisin', and hydrocortone ointment locally, and with vitamin B complex. He made a rapid recovery. In October he had another attack and was admitted to hospital. Investigation again showed a raised E.S.R. and eosinophilia. Swabs from his stomal ulcers grew *Staphylococcus pyogenes* sensitive to chlortetracycline, which he had with his intramuscular penicillin.

REPLY.—The Stevens-Johnson syndrome differs from the more common erythema multiforme only in its severity and its predilection for the mucous membranes. The etiology is unknown, although there are undoubted cases which are precipitated by drugs such as phenobarbitone and the sulphonamides, and others in which there is an associated virus infection such as virus pneumonia, infective hepatitis and glandular fever. I believe there is a connexion between herpes simplex infection of the skin and mouth and erythema multiforme though there is as yet no laboratory confirmation of this. In the present case, a herpes stomatitis could have been the precipitating cause. My experience of the severe cases of Stevens-Johnson syndrome has confirmed W. F. Lever's observation (*Arch. Derm. Syph.* (*Chicago*), 1944, **49**, 47) that if recurrent attacks occur the subsequent attacks become milder, and this is borne out in the above history. When there are recurrent attacks it is important to exclude a drug allergy, and the patient should be asked specifically about barbiturates and laxatives containing phenolphthalein. I know of no way to prevent the recurrent attacks of erythema multiforme but fortunately few patients continue to have severe attacks for more than two to three years.

In the treatment of the attack, local chlortetracycline ('aureomycin') paint (250 mg. suspended in 10 ml. of water) to the mouth lesions is a help, and chlortetracycline, 250 mg. six-hourly by mouth, has appeared to improve some of my cases though not all. The sulphonamides and antibiotics, other than chlortetracycline, have not been of benefit in my hands and in view of the possible allergic basis of the condition are better avoided. The evaluation of treatment is always difficult as the Stevens-Johnson syndrome is a self-limiting disease which improves spontaneously in ten to fourteen days, but corticotrophin and cortisone are logical remedies if one believes that the condition is an allergic skin reaction, and there have been several reports of speedy recovery with their use. It would seem well worth trying cortisone in the present instance immediately there is a sign of a recurrence. A dosage of 200 mg. at the start and 100 mg. daily for four to five days would be reasonable.

I. B. SNEDDON, M.B., M.R.C.P.

Paget's Disease of Bone

QUERY.—I should like to ask a question in respect of Paget's disease of bone. The patient is a man, aged 52, who presented himself complaining of pain over the middle third of his left tibia. His x-ray is characteristic of Paget's disease. I have always understood that no treatment was of any avail in arresting the disease, and a recent search of the literature would tend

to confirm this. However, as he is the earliest case which I have seen in 28 years of practice, I should like to assure myself regarding treatment.

REPLY.—There is no treatment of proved value for Paget's disease of bone (osteitis deformans). Pain in the tibia is often due to deformity and can be relieved by osteotomy. Methyltestosterone, 10 mg. thrice daily, seems to decrease the amount and severity of pain in some patients.

D. TAVERNER, M.D., M.R.C.P.

Assessment of Ascorbic Acid in Foods

QUERY.—How can the diet of a large institution be simply examined to find if it contains adequate ascorbic acid after cooking? What are the common symptoms of mild ascorbic acid deficiency and are there any chemical tests which can be applied to blood or urine to prove either adequacy or insufficiency of this substance?

REPLY.—It is relatively simple to determine, with sufficient accuracy for this purpose, the amount of ascorbic acid in foods. In practice, however, it is probably best to look into the general question of the purchase, cooking and serving of the meals. From this, one can get quite a good idea of whether the vitamin is being unduly depleted in the diet and also have the information which will enable one to suggest ways to avoid this depletion.

The main sources of vitamin C are green vegetables, potatoes and fruit (other than dried). The first thing to ensure, of course, is that sufficient of these are included in the menus. Secondly, it is necessary to see that the inevitable losses occurring during preparation and cooking are reduced to the minimum. As regards vegetables, loss of the vitamin begins at harvesting, so that old and wilted vegetables must be avoided. During preparation of the vegetables, destruction is increased if they are inordinately bruised. During cooking, loss of the vitamin occurs partly by oxidation and partly by leaching into the water. The former may be reduced by: (1) rapid initial heating, for example starting with boiling water (which rapidly destroys the oxidizing enzyme); (2) cooking in a minimum of water; (3) cooking for the shortest possible time. Destruction after cooking continues while the vegetable is kept hot before serving, so that this interval must be made as short as possible. As regards potatoes, the main source of loss is in keeping them hot, especially if they are mashed and therefore have air mixed with them.

Mild ascorbic acid deficiency is indistinguishable from a variety of other early deficiencies and indeed from general ill health due to other causes. The symptoms include weakness, lassitude and listlessness and there may be shortage of breath and aching of the limbs.

Chemical methods for determining deficiency depend upon the estimation of vitamin C in the urine after test dosing, or in the whole blood or in the white cells. The most difficult, but the most accurate, of these is the last, but even here one must remember that there are individual variations. References to appropriate methods may be found in such a book as Bicknell and Prescott's 'The Vitamins in Medicine', published by Heinemann.

PROFESSOR JOHN YUDKIN, M.D., M.R.C.P.

PRACTICAL NOTES

Penicillin V

'IT appears that many of the infections that have been treated parenterally with penicillin in the past may now be treated with penicillin V given orally' is the conclusion reached by W. J. Martin *et al.* (*Proceedings of the Staff Meetings of the Mayo Clinic*, October 19, 1955, **30,** 467) as the result of their investigations which included its use in 30 patients with various infections. The advantage of penicillin V, compared with penicillin G, is that it is acid resistant and therefore passes through the stomach unchanged, to be absorbed in the alkaline medium of the small intestine. Following oral administration of penicillin V, detectable amounts are present in the serum for at least four hours. The recommended dose, given four-hourly, is 200,000 units for minor infections, 400,000 for infections of moderate severity, and 800,000 units for fairly severe infections. The only side-effect so far encountered at all frequently has been 'mild gastrointestinal irritation manifested by slight abdominal cramping and an increased number of stools that tend to be liquid in character'. One patient developed 'rather severe aphthous stomatitis that ostensibly was due to the agent'.

A New Hypnotic

'NOLUDAR' (2, 4-dioxo-3, 3-diethyl-5-methylpiperidine) is 'a safe and effective sedative-hypnotic', according to L. J. Cass *et al.* (*New England Journal of Medicine*, October 6, 1955, **253,** 586). In a series of 31 patients with severe

insomnia the effects were compared of a placebo tablet, 500 mg. and 750 mg. of 'noludar'. The average time required to fall asleep with the placebo tablets was 2½ hours, compared with 40 minutes with 500 mg. of 'noludar' and 26 minutes with 750 mg. The only side-effect was temporary headache which was complained of by four patients. The effect of prolonged administration of massive doses of the drug indicated that there was no toxic effect on the hæmopoietic or urinary system. In a further trial, a series of 285 chronically ill patients, aged 25 to 95 years (average, 57 years), who required hypnotics, was given 200 mg. of 'noludar'. This produced a 'comfortable night's rest' in 243 cases; the remaining 42 patients responded satisfactorily to 400 mg. In general, sleep was induced in thirty minutes, and no side-effects were encountered.

Nitroglycerin Ointment in Angina Pectoris

On the recommendation of Professor Tinsley R. Harrison, J. A. Davis and B. H. Wiesel (*American Journal of the Medical Sciences*, September 1955, **230**, 259) have investigated the efficacy of nitroglycerin in the form of a 2% ointment in the treatment of angina pectoris. The ointment was supplied in 1-ounce (31 g.) tubes because, as in the case of nitroglycerin tablets, there is some evidence of deterioration on exposure to air. The ointment was applied with a wooden applicator to the chest wall on an area of 5 to 8 inches (13 to 20 cm.) in diameter. The recommended initial dose is ½ inch (12.5 mm.) of the ointment applied three or four times daily. The dose is subsequently adjusted to the patient's requirements. The estimated amount of nitroglycerin is 15 mg. in each ounce of ointment. Headache is a common side-effect initially, but this tends to become less frequent in the course of time. In the 17 patients on whom the effect of the ointment was tried, all of whom had previously been on nitroglycerin tablets, the results of the ointment were assessed as good in nine, fair in four and poor in four. Typical of the good results was the patient who before using the ointment had required one to seven tablets daily but while using the ointment never required more than one a day, whilst another patient who previously had required eight to ten tablets daily, subsequently never required more than two daily while using the ointment.

Pancreatin in Fibrocystic Disease of the Pancreas

The absorption and utilization of fat and protein in children with fibrocystic disease of the pancreas are improved by pancreatic therapy, according to Ruth Harris, A. P. Norman and W. W. Payne (*Archives of Disease in Childhood*, October 1955, **30**, 424). Balance studies were carried out on 12 children, typical examples of fibrocystic disease, who had been under observation for some years at The Hospital for Sick Children, Great Ormond Street. The results were compared of the children receiving no pancreatin, 5 g. of pancreatin with each meal, and 15 g. with each meal. The pancreatin was given four times daily immediately before each meal, and was usually swallowed dry or stirred into a little cold milk or water. The preparation used was powdered pancreatin (B.P. triple strength) treated to form enteric-coated granules. As shown by gain in weight, positive nitrogen balances and increased fat absorption, pancreatin improved the absorption and utilization of fat and protein: 5 g. of pancreatin with each meal is probably the largest dose required.

Reserpine and Chlorpromazine in Psychiatry

As a result of their experience with over 300 patients, J. A. Barsa and N. S. Kline (*Archives of Neurology and Psychiatry*, September 1955, **74**, 820) conclude that 'combined reserpine-chlorpromazine therapy is effective in chronically disturbed psychotic patients'. Their dosage schedule was as follows. The initial dose was 3 mg. of reserpine and 25 mg. of chlorpromazine orally once a day. If there was no satisfactory progress after three to four weeks the dose of chlorpromazine was increased to 50 mg. twice daily. If after another month's treatment, progress was still not satisfactory, 5 mg. of reserpine intramuscularly was added to the daily regimen. This intramuscular dose of reserpine was doubled after ten days if necessary. When an adequate response was obtained, intramuscular medication was gradually reduced, but oral treatment was maintained for a minimum of three months. Toxic effects included convulsions (1 case), Parkinsonism (3), jaundice (4), and agranulocytosis (2). All recovered. It is stated that the results with this combined therapy were better than with either reserpine or chlorpromazine alone.

Chlorpromazine in Cerebral Palsy

Promising results are reported by E. Denhoff and R. H. Holden (*Journal of Pediatrics*, September 1955, **47**, 328) from the use of chlorpromazine in a small series of 18 children (aged 1 to 12 years) with cerebral palsy. The drug was given in the form of an orange-flavoured syrup, each 5 ml. of which contained

10 mg. of chlorpromazine hydrochloride. Children up to 5 years of age received 10 mg. thrice daily; older children received 20 mg. thrice daily. After a month's treatment, nine of the 18 children (50%) showed improved behaviour with chlorpromazine, compared with only three (17%) while on a placebo. All four children classified as having 'body anxiety' showed improvement, but only one of the four children who were anxious because of environmental stress alone. Four of the 10 children rated as 'non-anxious' improved by 'being more relaxed behaviourally'. In 17 of the children treatment with chlorpromazine was continued for periods ranging from one to ten months (mean, 4.3 months), and it is reported that 'eleven of these children continued to improve in physical and emotional adjustment'. No toxic effects were noted.

Chlorpromazine Dermatitis

A 'no touch' technique in the dispensing of chlorpromazine is strongly recommended by H. Lewty, chief pharmacist to a mental hospital in Lancashire (*Pharmaceutical Journal*, November 12, 1955, **175**, 463). In this hospital, which has a nursing staff of 425, there have been 11 cases of severe contact dermatitis due to chlorpromazine among the women and two among the men. In addition, one out of the six members of the pharmaceutical staff has been similarly afflicted. The areas usually affected are the face, especially round the eyes, the neck and between the fingers. There is swelling, erythema and intense pruritus. Later, the skin may peel off, and in some cases the new skin readily breaks down again. In some cases the sensitivity is so marked that contact with perspiration or droplets of saliva from a patient taking the drug will provoke an attack. It is stated that 'once a person is sensitized there is no other course than to keep right away from the drug . . . Patch testing for sensitivity is quite dangerous'. Antihistaminics are of little value in treatment, but hydrocortisone ointment or lotion helps to allay the severe inflammation.

Radiotherapy of Carcinoma of the Lung

'THE conclusion seems inescapable that radical radiotherapy' for carcinoma of the lung 'can only be justified, if at all, in very stringently selected cases', according to W. M. Levitt (*British Journal of Tuberculosis*, October 1955, **49**, 260). This is not only because of the poor results, but also because of 'the considerable constitutional reactions and the risk of damage to structures in the neighbourhood of the growth' which accompany its use. The contraindications to radical irradiation are listed as follows:—(1) Oat-celled carcinoma and other undifferentiated growths. (2) Deterioration in the general condition of the patient out of proportion to the strictly localized growth. (3) Unexplained pyrexia. (4) Persistent unexplained tachycardia. (5) Severe persistent and unexplained thirst. In the author's experience this last feature is 'one of the most valuable signs of liver involvement'. Palliative radiotherapy is indicated when there is threatened or actual mediastinal obstruction, when there is persistent hæmoptysis, and when pain is a marked feature. Contraindications to palliative radiotherapy are a large pleural effusion which rapidly reaccumulates after tapping, infection, and disease which is too extensive to offer any hope of being covered with useful dosage. On the other hand, the call for relief of symptoms—e.g. mediastinal obstruction—may be so urgent that palliative treatment may be worth while even in the presence of generalized secondaries. Reference is made to the possible value of cortisone or corticotrophin as a means of reducing the side-effects of irradiation. For this purpose these preparations should not be given until several months after the completion of irradiation. Radiotherapy is of 'much palliative value' in the treatment of secondary deposits in bone and in the brain.

Nalorphine in Depression of the Newborn

THE dangers and disadvantages of the routine administration of nalorphine to the parturient mother as a prophylactic against neonatal depression of the newborn are discussed by B. A. Greene (*American Journal of Obstetrics and Gynecology*, September 1955, **70**, 618). It is pointed out that nalorphine is a mild narcotic capable of depressing respiration and circulation. It is not effective in counteracting depression produced by ether, cyclopropane or barbiturates, and it increases the depression of mothers sedated with quinalbarbitone sodium and pethidine. Further, nalorphine has little analeptic effect, and its action on respiration usually disappears before that of pethidine or morphine. The position is summed up as follows. 'The routine use of nalorphine in the parturient mother, either with each dose of narcotic or ten to twenty minutes before delivery, is unjustified because (1) only a small minority of narcotized mothers give birth to depressed infants, (2) in the absence of general anæsthesia the incidence and management of neonatal asphyxia are not significantly improved by nalorphine, (3) in the presence of general

anæsthesia the benefit of nalorphine is not evident; it tends to prolong maternal depression, and after ether to aggravate neonatal depression. On the basis of present evidence the most practical and effective method of administering nalorphine is by umbilical vein only when required. . . Nalorphine should be avoided when neonatal respiration and/or circulation are depressed primarily by causes other than narcotics'.

Ingrowing Toenails

A METHOD of treating ingrowing toenails which, he claims, 'will cure every case, infected, or otherwise, complicated or uncomplicated, without fail, without hospitalization and without absence from work' is described by George Sacks (*South African Medical Journal*, October 8, 1955, **29,** 976). If the case is infected, the lateral skin-fold is gently pushed from the nail with a wisp of cotton-wool at the end of a flat probe. This space is then packed with a little cotton-wool soaked in bipp (bismuth-iodoform-paraffin-paste). The space under the growing edge of the nail is similarly packed. The whole toe is then covered with 'elastoplast' like the finger of a glove. The 'elastoplast' makes the skin underneath sodden and this is what is required. Two to three days later the 'elastoplast' is removed, the toe is cleaned with spirit, and the packing is repeated. This process is repeated until the whole of the offending corner of nail is lifted easily to ride over the skin edge. After two to three weeks the close 'elastoplast' cover is replaced by spirit soaks and an 'elastoplast' cover which does not seal off the toe from the air, and this allows the toe and skin to harden. At the end of six weeks 'the patient is left with a normal toe'.

Advice for the Itinerant Invalid

THE following are some of the axioms propounded by Professor W. C. Alvarez in a recent article entitled 'When sick people travel' (*International Record of Medicine*, August 1955, **168,** 520). 'He whose heart is good enough so that he can walk comfortably on the street can fly in an airplane'. 'Persons who suffer from a gall-stone colic should carry with them a sedative for pain. Those who suffer from angina pectoris should carry tablets of nitroglycerin; those who suffer from asthma should carry perhaps a small atomizer with a strong adrenaline spray; and those who suffer severely from sick headaches should carry with them a number of pills of "cafergot"; they should take two of these the minute a spell threatens'. He advises patients with chronic arthritis to take with them a tablet containing aspirin, phenacetin, caffeine and codeine. 'Persons who have a little tendency to diarrhœa will do well to take with them some hard tablets of codeine (½ grain [30 mg.] each)'. For motion sickness he recommends 'some helpful drug, such as "dramamine" (dimenhydrinate) . . . or "marzine" (cyclozine)'. For those who are subject to colds he advises capsules containing codeine and papaverine (¼ grain [16 mg.] of each). 'One or two of these, taken as soon as the throat becomes raw or the nose begins to run, may stop the cold'. 'Many persons whose eyes are highly sensitive, and particularly the migrainous person, should use dark glasses when the sun is very bright'.

Prelaryngeal Bursitis

FIVE cases of what are considered to be a hitherto unrecorded condition are described by H. Loebell (*Münchener Medizinische Wochenschrift*, November 25, 1955, **97,** 1579). The condition, to which the author has given the name of prelaryngeal bursitis, is attributed to pressure caused by too tight a collar, or by wrestling, resulting in inflammation of the bursa in front of the larynx. The patient complains of pain on bending the head backwards or on swallowing. The only physical sign is slight tenderness over the middle of the larynx. Treatment consists of removal of the cause and the local application of heat.

Football Albuminuria

THE incidence of albuminuria before and after playing a game of football has been investigated by D. Selman and C. Gualano (*New York State Journal of Medicine*, November 1, 1955, **55,** 3120) in 27 high school boys aged 14 to 17 years. One of the boys had albuminuria before playing and it was still present after the game. Of the remaining 26 boys who had no albuminuria before playing, 24 (92%) had albuminuria after the game, ranging from a faint trace to 4 plus. All 27 specimens were free of sugar before the game; subsequently one specimen gave a positive reaction for glucose. Acetonuria was absent in all specimens before and after the game. None of the specimens examined before playing contained casts, but after the game 23 specimens (81%) contained hyaline and/or granular casts. Assessing hæmaturia as being present when at least 10 to 15 red cells were visible per high-power field, all pre-game specimens were clear, and hæmaturia was present in one post-game specimen. Subsequently this boy's urine became free from red cells on repeated examination. The rarity of hæmaturia in this investigation is attributed to: (i) the nature of the sport; (ii) the fact that no boy played more than 48 minutes; (iii) the fact that heavy protective hip pads were worn.

REVIEWS OF BOOKS

An Atlas of Regional Dermatology. By G. H. Percival, M.D., Ph.D., F.R.C.P.Ed., D.P.H., and T. C. Dodds, F.I.M.L.T., F.I.B.P., F.R.P.S. Edinburgh: E. & S. Livingstone Ltd., 1955. Pp. vii and 264. Figures 475. Price £5.

The publication of an atlas of coloured pictures for the use of the medical profession is necessarily a joint matter in which photographer, publishers and printers must share criticism and praise with the author; especially so in this case in which legends are reduced to a minimum and much depends upon the quality of reproduction of the original photographs. At the outset therefore it is a pleasure to be able to congratulate those responsible for 'taking' the original transparencies for the clarity, depth of focus and choice of pose of the photographs, and Messrs. Livingstone and the Darien Press for the very fine reproductions in full colour of which this book is composed. Although by modern methods red—which is the predominant feature in most of the illustrations—is not so difficult to control as formerly it is still not easy to reproduce accurately the many shades of this primary hue on paper: 'red', as the printers used to say, 'runs amok if it can', but in this work the quality of reproduction is excellent.

Of the work of the authors, it is difficult to be so warmly complimentary. They have selected, doubtless from a mass of material, a remarkable collection of photographs, but one is uncertain about their aim. Few consultants —unless they want to borrow the blocks for illustrations to adorn one of their own works— are likely to invest in a book of this type; registrars in all grades working in skin departments will find it useful; for the average practitioner and also for the medical student it contains far too much and they may find some of the illustrations misleading. For example, florid favus as shown in no less than five illustrations is an extreme rarity in most parts of the country; it is the chronic and relatively minor variety, which is not illustrated, which is missed and which deserves emphasis. One can examine scores of cases of scabies and yet not see anything resembling fig. 299. Pityriasis versicolor is excellently illustrated in fig. 340, yet fig. 339 which illustrates the same malady is so unusual that when it was shown to a colleague with the caption hidden he had to confess that he could not recognize the eruption: it might, he said, be one of several rashes which he named.

Then, too, there is the question of nomenclature: it is difficult to understand, even when the legends rather qualify the primary diagnosis, how the man with the red and crusted scalp and a pink ear, and also the man with a crusted eruption of the beard area, ear, mastoid zone and the back of the neck (fig. 51 and 53) are labelled flexural infective eczema. Even if the concept of seborrhœic eruptions varies between Edinburgh and other centres (and the views held in Edinburgh may eventually be proved correct and the others wrong), if the book is now to be widely appreciated a few explanatory notes (where they are absent) or rather fuller notes (where some are given) concerning the differences of nomenclature current in the leading schools should be added, for in practice one makes diagnoses merely to determine treatment, and the therapy of eczema and seborrhœic dermatitis can be quite dissimilar.

These caveats having been entered, there is much on which congratulations can be given: the four photographs of herpes zoster showing the changes in the eruption between the 3rd and 15th days, the series illustrating various forms of pemphigus, much of the group of dermatitis herpetiformis, fig. 347 of molluscum contagiosum (always difficult to photograph) and many of the photographs of syphilitic eruptions deserve special mention. The notes given in the captions are succinct and usually helpful. Finally, there is an adequate index.

Modern Trends in Obstetrics and Gynæcology (*Second Series*). Edited by Kenneth Bowes, M.D., M.S., F.R.C.S., F.R.C.O.G. London: Butterworth & Co. (Publishers) Ltd., 1955. Pp. xv and 407. Figures 176. Price 60*s*.

This volume is quite independent of the book with the same title published in 1950 and should be regarded as a companion volume. It consists of twenty-five chapters covering a wide field of diverse subjects of recent and topical interest. The contributors are recognized authorities and together they form a most distinguished and authoritative panel.

In these days of rapidly advancing knowledge the book will be of great help to the practising obstetrician and gynæcologist who wishes to keep abreast of the newer knowledge of his specialty. It will be welcomed by the advanced student, and its careful study can be recommended to those preparing for higher examinations in obstetrics and gynæcology although the book is not in any sense written with this in mind. The general practitioner whose interest leans towards obstetrics and gynæcology will find much of great interest to him. Whilst some

chapters are highly scientific, others, such as the forceps operation in modern obstetrics, acute abdominal conditions in pregnancy and the puerperium, establishment and maintenance of respiration in the newborn, and emergency surgery in the newborn, are written from a thoroughly practical and clinical standpoint. The book fulfils its purpose well, but a contribution on acquired afibrinogenæmia would have been a welcome addition..

Polycythemia. By JOHN H. LAWRENCE, M.D., D.Sc., F.A.C.P. New York: Grune & Stratton Inc., 1955. Pp. 136. Figures 38. Price $5.50.

IN this small book the author summarizes his extensive experience of polycythæmia and reviews the recent literature on the subject. As might be expected most of the book is devoted to polycythæmia vera, but space is also given to relative polycythæmia and secondary polycythæmia. Consideration is given to the clinical features of these diseases as well as to laboratory studies and treatment. The author supports the view that polycythæmia vera is a neoplastic-like disease associated with an increased rate of red cell production and with a reduction in red cell survival. He rejects the suggestion that the condition is the result of bone marrow hypoxia. Lawrence is a pioneer in the use of radioactive phosphorus in the treatment of polycythæmia vera, and his extensive experience with this form of therapy has served to confirm his view that for most patients this is the treatment of choice. The book is liberally illustrated with graphs and charts, and there are two colour photographs. In one of these the cyanosis of the patient is overshadowed by her lipstick and nail varnish. There is an admirable bibliography of 209 references. This book is highly recommended to all who wish to have an up-to-date review of these diseases.

Cough Syncope. By VINCENT J. DERBES, M.D., F.A.C.P., and ANDREW KERR, JR., M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1955. Pp. viii and 182. Figures 7. Price 34*s*.

COUGH syncope is an episode which is not sufficiently recognized by the medical profession in Great Britain. It is doubtful, however, if this symptom complex warrants the writing of a monograph of some 170 pages. The condition is important because it must be differentiated from other more serious causes of transient loss of consciousness, thus saving the patient from much unrewarding investigation, and a possible unjustifiably gloomy prognosis. If it is remembered that the syncope can occur in association with a single cough as well as after a paroxysm, and that the victim is nearly always a male, the diagnosis should not be difficult. If, in addition, the man is a bronchitic, with emphysema and bronchospasm, and likes his smoke, his drink and his laugh, then the diagnosis is almost certain. Any publication which stresses these limited facts is valuable, but thirty-six case histories would seem to be rather an extravagance: a few typical such histories would have been more effective. Some thirty pages are devoted to the physiological mechanisms of the syncope and the conclusion is reached that pulmonary vasospasm and peripheral vasodilatation probably play a part.

It is to be hoped that the simple descriptive name 'cough syncope' will never be superseded by 'tussigenic syncope', a term often used as an alternative in the letter-press of this rather ponderous monograph.

Fluoroscopy in Diagnostic Rœntgenology. By OTTO DEUTSCHBERGER, M.D. Philadelphia and London: W. B. Saunders Co., 1955. Pp. xvii and 771. Figures 517. Price £7 14*s*.

THE express purpose of this book is 'to compile all the essential knowledge about fluoroscopy in a single complete volume. This book is also the first critical approach to the potentialities and limitations of the fluoroscopic method. Thus, it should be helpful not only to the student of medicine and the clinician, but also to the rœntgenologist and to the specialist in fields other than rœntgenology'. This quotation from the preface largely expresses the difference in outlook between the United States and Great Britain in the practice of radiology. Many general practitioners in the United States have x-ray units in their offices, but such an arrangement is looked upon with disfavour in this country. The heart of the book is really confined to the chapter on the 'Hazards of fluoroscopy' (pp. 66 to 77). This is a subject which should be compulsory reading for anyone using, or intending to use, x-ray equipment for fluoroscopy. Radiologists in general are much exercised by the widespread use of fluoroscopy by specialists who have no radiological training and who do not understand the dangers involved. One would like to see this chapter reprinted, and issued by x-ray manufacturers with every fluoroscopic unit to be used by specialists other than radiologists. For no other reason than this, the book is well worth while. In addition, there is much useful information regarding equipment for fluoroscopy including the more recently introduced image amplifier, which is

unlikely, however, to have much use in private practice.

As a basic textbook of radiology, it can be recommended and it is well documented with references so that further reading in any particular aspect of the subject can easily be followed up. The book is well produced and profusely illustrated. The x-ray illustrations are in the less popular form of positive prints, but are of good quality and the type is easy to read and pleasing to the eye. To all who are in need of instruction and guidance in fluoroscopy in radiology, this book can be well recommended.

Dermatologie der Mundhöhle und der Mundumgebung. By Dr. Aloys Greither. Stuttgart: Georg Thieme, 1955. Pp. xvi and 262. Figures 191. Price DM 39.60.

This is an excellent book and can be highly recommended. The mouth is the meeting ground of dermatologist, throat specialist, dentist, surgeon, and general physician, but as a special subject has been rather neglected, and there is no other book known to the reviewer that covers the ground so well. The writing is expert and scholarly. Clinical descriptions are so clear that the many good illustrations in black and white add little; one misses colour. There are instructive sections on the normal histology of the oral mucosa and on the bacterial flora of the mouth. Not surprisingly, one may find some anomalies. Thus, only one page is allowed for lepra, whilst equal space is given to gonorrhœa, to establish that gonorrhœa of the mouth does not occur.

The book is beautifully and accurately printed. Rather a high proportion, however, is in small type. This occasionally includes the recommendations for treatment, the value of which is sometimes impaired by the use of unknown proprietary names.

The Biologic Effects of Tobacco. Edited by Ernest L. Wynder, M.D. Boston: Little, Brown & Co.; London: J. & A. Churchill Ltd., 1955. Pp. xiii and 215. Figures 19. Price 32*s*.

As Dr. Joseph Garland comments in his foreword to this book, 'to smoke or not to smoke has become one of the burning issues of the day'. It is therefore not surprising that publishers are falling over each other in attempting to supply the protagonists in this topical controversy with the requisite literature. For those who wish to obtain a concise, balanced and unbiased summary of the available data this book can be thoroughly recommended. The first two chapters deal with the chemistry and pharmacology of tobacco. Then follow chapters dealing with the effect of smoking on the cardiovascular system, neoplastic disease, and the gastro-intestinal tract. There is also a chapter on allergy to tobacco, and finally a review of the statistical evidence. Throughout the emphasis is on the clinical aspects of the subject, and the eight collaborators have been particularly successful in their task.

Arctic Doctor. By Dr. Joseph P. Moody. London: Odhams Press Ltd., 1955. Pp. 256. Illustrations 15. Price 15*s*.

Soon after qualifying, in 1946, Dr. Moody accepted an appointment as a medical officer in the Canadian Government's arctic medical service. In this book he recalls some of his more outstanding experiences. With the discovery of uranium and other rich metallic deposits the Canadian East Arctic is now undergoing a rapid transformation, but even ten years ago it still presented many hazards, and Dr. Moody had his full share of them. This, however, is not merely an adventure book. The author gives an admirable, and sympathetic, description of the Eskimos and of their way of life. The medical interest is so interwoven with the rest of the story that the book will appeal to the layman as much as to the doctor. The latter, however, will particularly appreciate the author's account of how he tracked down the origin of the epidemic which caused such havoc among the Eskimos during his period of service in the area. 'Arctic Doctor' will appeal to all discriminating readers, but it would have appealed even more if the reader had been supplied with a map of the area.

NEW EDITIONS

Modern Operative Surgery, edited by the late G. Grey Turner, D.Ch., M.S., F.R.C.S., and by Lambert Charles Rogers, M.D., M.Sc., F.R.C.S., F.R.C.S.Ed., volume I in its fourth edition (Cassell and Co. Ltd., 70*s*.) deals with orthopædics, amputations, thoracic surgery, operations on the spinal cord and on the peripheral nerves, vascular and cardiac surgery, the principles of operative treatment in malignant disease, operations on the breast, and operations on the abdominal viscera. This book has established so secure a place in the literature of British surgery, that the new edition is certain of its welcome. The first volume is largely rewritten. Stanley Evans, Jackson Burrows, Oswald Tubbs, George Mason and Norman Tanner all appear as authors of chapters for the first time, but the sound common sense and practical outlook that have always characterized the book remain unchanged. Particularly helpful is Grey Turner's advice on such fundamental subjects as prepara-

tion for operation, the choice of operation in relation to the lesion and the patient, the dangers to be avoided, and after-care. Compared with some other books on operative surgery the figures are sparse and often old-fashioned. Some of the illustrations of well-known instruments from makers' catalogues could well be omitted.

A Short Textbook of Surgery, by C. F. W. Illingworth, C.B.E., M.D., CH.M., F.R.C.S.ED., in its sixth edition (J. & A. Churchill Ltd., 37*s.* 6*d.*) has undergone considerable change in a laudable attempt to 'rationalize the clinical approach' by giving less attention to detail and more to general principles. This is a move in the right direction in the case of a book such as this which is intended primarily for students. It is perhaps ungracious to say that the process has not been carried far enough. The new section on the surgery of the heart, for instance, would have been an excellent opportunity to have given the student the essential facts that he requires in deciding whether or not a patient is a suitable candidate for surgery: the rationale of the operation, the indications and the prognosis. There is an unfortunate misprint in the index in the last entry under 'G'. This, however, remains an excellent introduction to surgery for the undergraduate.

Diseases of The Nose and Throat, by Sir StClair Thomson, M.D., F.R.C.P., F.R.C.S., revised by V. E. Negus, M.S., F.R.C.S., with the assistance of G. H. Bateman, B.M., F.R.C.S., in its sixth edition (Cassell & Co. Ltd., 90*s.*) has undergone radical revision. Although it is thirteen years since Sir StClair Thomson died, his name is still retained on the title page. It is only fair to say, however, that the credit for the excellence of this edition—and excellent it is—is due to Mr. Negus and Mr. Bateman. The only criticism is of the sections on syphilis, many of which are sadly out of date. This remains, however, the outstanding British book on the subject—comprehensive yet discriminating, authoritative but never biased.

Heart Disease, by E. Goldberger, M.D., in its second edition (Henry Kimpton, 92*s.* 6*d.*) has been carefully revised. It is not, however, a book that can be recommended to the learner. In the attempt to be comprehensive the author has ceased to be selective. The short paragraph on the etiology of auricular fibrillation (p. 366) is an excellent example, and the initial paragraph on drug therapy in angina pectoris (p. 304) is a masterpiece of therapeutic impartiality. In the chapter on rheumatic heart disease, mitral incompetence is given priority over mitral stenosis. The style also is not above criticism: e.g. 'The concept of "blood pressure" and especially the significance of minor fluctuations should be de-emphasized to the patient'. Most of the essential information is in this book, but it requires considerable experience to be able to translate it into safe practice.

Psychological Medicine, by Desmond Curran, M.B., F.R.C.P., D.P.M., and Maurice Partridge, D.M., D.P.M., in its fourth edition (E. & S. Livingstone, Ltd., 21*s.*) has been expanded to meet recent developments and to include additional details of specialized treatments. The whole has been revised and much of the text rewritten. A feature is its eminently practical and balanced orientation to clinical psychiatry for the beginner. The salient features of the common syndromes are lucidly described, together with an essentially realistic outline of the means of investigation and treatment. There is a commendable section on anxiety states, drawing attention to the indiscriminate use of the term and rightly emphasizing its frequent association with depression. The references to psychoanalysis may be open to the criticism that they do less than justice to the contributions of this school. As an introduction to the subject this book can be recommended without reservation. It presents the elements of clinical psychiatry clearly and concisely. If students and practitioners were to master the basic ideas and practical measures embodied in the text they would surely deal more effectively with those who seek their help.

The Care of Young Babies, by John Gibbens, M.B., M.R.C.P., in its fourth edition (J. & A. Churchill Ltd., 6*s.*) is a sensible little book that can safely be recommended to the mothers and fathers for whom it is written. It is admirably balanced but perhaps insufficiently dogmatic for the mother who wants to be told exactly what to do; for example, rectal temperature taking is advised but no instruction given, the thermometer illustrated is of the thin-bulbed oral type. The modern views on circumcision and umbilical hernias are emphatically expressed.

The contents of the February issue, which will contain a symposium on 'Neurology' will be found on page c at the end of the advertisement section.

Notes and Preparations, see page 113
Fifty Years Ago, see page 117
Motoring Notes see page lxxxiii

BINDING CASES

Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 3*s.* each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 12*s.* 6*d.* per volume; this includes the cost of the binding case and return postage.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

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'SUAVITIL' tablets each contain 1 mg. of benactyzine hydrochloride and are intended for the treatment of psychoneuroses arising from external stress, particularly those with anxiety reaction. Available in bottles of 100 sugar-coated tablets. (Glaxo Laboratories Ltd., Greenford, Middlesex.)

PHARMACEUTICAL NOTES

SMITH KLINE & FRENCH INTERNATIONAL CO. announce the introduction of 'drinamyl spansule' capsules. One capsule taken on rising 'affords day-long control of worry and harassment'. Available in two strengths: no. 1 containing 10 mg. of 'dexedrine' and 65 mg. of amylobarbitone, and no. 2 containing 15 mg. of 'dexedrine' and 97 mg. of amylobarbitone. Both strengths are available in containers of 30 capsules. (Coldharbour Lane, London, S.E.5.)

FILM NEWS

Therapy with Cortone (*cortisone acetate*) (16 mm., colour, sound; running time 30 minutes) surveys the results secured with 'cortone' in patients suffering from rheumatoid arthritis, pemphigus, traumatic iritis, asthma and rheumatic fever. *The Technique of Joint Aspiration and Injection of Hydrocortisone* (16 mm., colour, sound; running time 12 minutes) presents the technique of joint aspiration and the intra-articular injection of hydrocortisone. Both these films are available for showing to medical and pharmaceutical groups and may be had on application to Merck-Sharp & Dohme Ltd., who can also offer the services of a medical lecturer to introduce the films. (Hoddesdon, Hertfordshire.)

N.A.P.T.

THE annual report of the National Association for the Prevention of Tuberculosis for 1954-55 covers as wide and variegated a field as ever. Under the ægis of the Association an investigation is being carried out into the psychology of the tuberculous patient, based upon a 'personality' study of 500 patients. Three films have been produced during the year: 'This Little World', 'Sanatorium Nurse', and 'BCG Vaccination against Tuberculosis'. These may be hired for 10s. a day or £2 a week. The resources of the Queen Alexandra Sanatorium Fund, which is controlled by the Association, are being used to provide high Alpine treatment for children with established and fairly severe asthma which has not responded to treatment in Britain. Parties of nine children are treated at a sanatorium at Davos, where they spend eighteen months. During the year two scholarships have been awarded to medical students in Leeds and London and grants made to medical students at the Scottish universities whose studies have been handicapped by tuberculosis. These are but a few of the many activities of this versatile and progressive organization. (National Association for the Prevention of

Tuberculosis, Tavistock House North, London, W.C.1.)

THE NUFFIELD TRUST

THE third report of the Nuffield Provincial Hospitals Trust, which deals with the period 1951-55, covers a wide variety of subjects, ranging from the provision of a new hospital for Alderney, through prescribing by general practitioners, to the cost of hospital laundries. For instance, the Trust has made a grant of £1,900 to the Cossham and Frenchay hospital management committee 'to assist the rationalization of laundry arrangements at Cossham hospital'. The justification for this expenditure is that it is estimated that the laundry services of the hospitals in England and Wales cost £8 million a year. The investigation into the prescribing of general practitioners under the National Health Service is being carried out by Professor R. M. Titmuss of the department of social science at the London School of Economics. But perhaps the most interesting of all the Trust's gifts is that of £20,000 towards the building of a new hospital in Alderney—'the only part of the United Kingdom which was actually occupied during the 1939-45 War'. As Alderney was entirely evacuated during the war, it suffered almost complete ruin at the hands of the Germans without the compensation which came to Jersey and Guernsey in the form of the British Government's honouring of German debts. (Nuffield Lodge, Regent's Park, London, N.W.1.)

GENERAL PRACTICE IN SCOTLAND

THE number of family doctors in Scotland on June 30 last year was 2,568, of whom 60% were in partnerships, according to the seventh annual report of the Scottish Medical Practices Committee. It is noted that there are three ways for a doctor to become established as a principal in general practice: he may apply for an advertised vacancy, set up a new single-handed practice, or join in partnership with an already established practitioner. The last of these, after a preliminary assistantship, is strongly recommended. Young doctors seeking a post are advised to look upon the advertised vacancy, 'not as the main, or best, method of entry into general practice, but as an additional method while they are attempting one or other of the alternative methods'. In discussing the setting up of a new single-handed practice, it is pointed out that few people will take the trouble to apply for a change of doctor and there is less fluidity than in the pre-N.H.S. days. Further, newcomers to a district are more likely to be attracted to larger established practices than to a young doctor who has still to make his name.

TOXOPLASMOSIS

HITHERTO there has been only one reference expert for the examination of sera from suspected cases of toxoplasmosis. In view of the increasing interest of practitioners in this disease, a second reference expert has now been appointed. Laboratories in the south of England are asked to send sera to The Clinical Pathologist, The Hospital for Sick Children, Great Ormond Street, London, W.C.1 (Tel.: Holborn 9200), and laboratories in the north of England to Professor C. P. Beattie, Department of Bacteriology, The University, Sheffield (Tel.: Sheffield 27451). It is particularly requested that each serum should be accompanied by a note on the age and sex of the patient, and the outstanding features of the clinical disease.

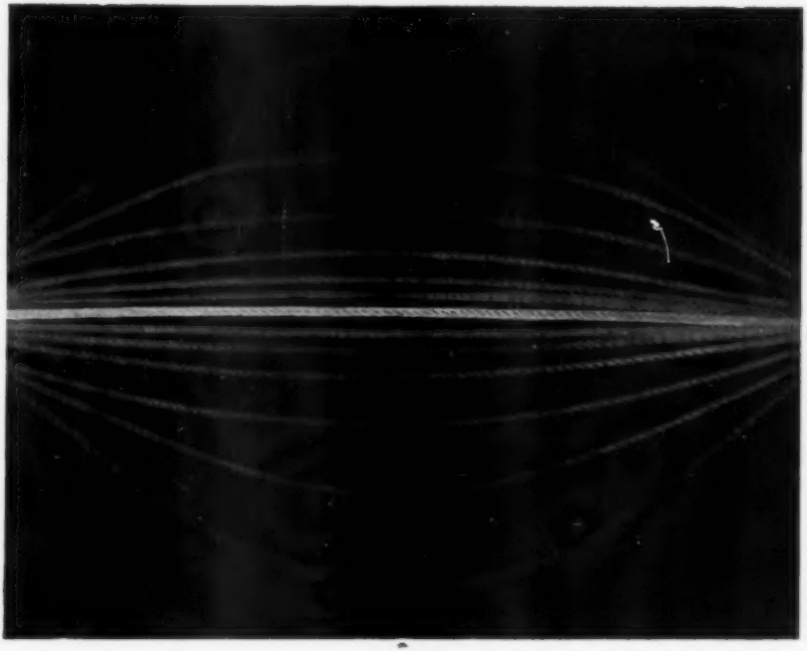
RETURN OF MEDICINE BOTTLES

THE Ministry of Health is anxious to obtain the cooperation of practitioners and pharmacists in trying to salvage some of the 100,000,000 medicine bottles which are issued every year for National Health Service prescriptions. Very few of these find their way back to the pharmacist. If patients would return their medicine bottles there would be a considerable saving to the country. Only standard medicine bottles (given on prescription) are wanted and, as no deposit is charged on bottles, no payment will be made for their return. Patients are requested to clean the bottles by washing them with hot soapy water before returning them. As part of a national publicity campaign the Ministry has issued a counter card to pharmacists, asking patients to return their bottles.

NEUTRALIZING FOG

ON the grounds that much of the pulmonary irritation caused by fog is due to sulphur acids, the Department of Scientific and Industrial Research is carrying out an investigation at St. Bartholomew's Hospital this winter to discover whether this action of fog can be neutralized by the inhalation of small amounts of ammonia gas. Patients with chronic bronchitis are being supplied with a bottle containing a solution of ammonia and a wick which can be pulled up and the ammonia gas thereby released into the atmosphere of the room. To ensure that sufficient, but not too much, ammonia gas is released, a special paper is supplied with the bottle. If the atmosphere is too acid this paper turns red; if too much ammonia is being released it turns blue, whilst the correct balance is shown by the paper becoming greenish-yellow. It is hoped that by this simple method many of the harmful effects of fog on patients with chronic bronchitis may be prevented, or at least alleviated.

CONTINUED ON PAGE 115



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THE FOOD WE EAT

THE extent to which chemicals, in the form of colouring matter, emulsifiers and preservatives, are being added to food was discussed at a recent W.H.O. conference in Geneva. Surveys indicate that in the United States over 800 chemicals have been recommended as food additives, whilst in Sweden 500 are in current use. A list prepared in Germany is said to contain over 1000 of these substances. The problem of colouring additives is particularly important as there are over 2000 synthetic dyes which might be used for this purpose. Fortunately, only about 80 of these are currently permitted in food. There are, however, no internationally agreed lists for either natural or synthetic colours, although attempts have been made to obtain international acceptance in Europe of a list of seven synthetic and five natural colours.

MODERN PARENTHOOD

'ZEST is required for family-making, as well as health and housing, employment and in-laws; nurses and doctors are in the position to foster this zest for living in the minds of young parents. Our interest in their youngsters must be personal, our guidance attractive without browbeating, and if possible, our own example may help to sell the idea that there is no adult fun on earth like a family. The ideal clinic doctor and the ideal health visitor are maybe the ones with happy children of their own. All this, however, will fail to touch those couples whose sole interest in parenthood seems to be to prove their own fertility by conceiving a single offspring, and then lapsing into ostrich-eyed aversion from the tasks and skill of child-nurture. The escapism of a father and mother both working full (and differing) shifts, in mills, and on buses, bears hard upon the waif on grandmother's doorstep'. Dr. C. C. Harvey, County Pædiatrician, in the annual report for 1954 of the Medical Officer of Health for the West Riding of Yorkshire.

MILK-BORNE TUBERCULOSIS

THAT 'the long drawn-out battle for safe milk —or at least for tubercle-free milk—has been virtually won' is the claim of W. A. Lethem of the Ministry of Health (*Monthly Bull. Minist. Hlth (Lond.)*, 1955, **14**, 144). The claim is based upon a comparison of the figures for the deaths from abdominal tuberculosis in children under five years of age in 1921 and in 1953. In 1921 there were 1,107 such deaths, compared with 12 in 1953. In 1921 the rates per million for such deaths were 136 in London, 437 in county boroughs, 336 in urban districts, and 252 in rural districts. In 1953 the comparable figures were 4, 1, 1, 12. These figures are correlated with the pasteurization of milk. In 1921, about 50% of the milk in London was pasteurized and much less in rural areas. In 1953, practically 100% of milk in London was pasteurized, whilst in England and Wales the figure was 88%.

PUBLISHERS' CATALOGUES

THE January 1956 catalogue of Messrs. E. & S. Livingstone (15-17 Teviot Place, Edinburgh, 1) has now been published. The 1955-56 catalogue of Pitman Medical Publishing Co. Ltd., (45 New Oxford Street, London, W.C.1) is also available. Copies of these two comprehensive catalogues can be obtained on application to the publishers.

PUBLICATIONS

The Princes in The Tower and Other Royal Mysteries, by Sir Arthur S. MacNalty, K.C.B., D.M., F.R.C.P., F.R.C.S., deals with ten historic mysteries, involving the Royal Houses of England, Spain, France, Sweden, Denmark and Russia. Some of them, such as the story of the Princes in the Tower, are well known; others, such as the death of the Duke of Bourbon, will be new to many readers. Throughout, the emphasis is upon the medical aspects. Taken together they provide provocative reading which will appeal to many readers. These selected frailties of royalty throughout the ages do not make pleasant reading but, as related here, they provoke sorrow rather than anger. (Christopher Johnson Publishers Ltd., price 18*s*.)

The Pack, by John Rowan Wilson, is a novel based upon life in a provincial teaching hospital. The author studied medicine at the University of Leeds and became F.R.C.S. in 1952. Leeds graduates will be able to tell whether or not there is any resemblance between the hospital described here and their teaching hospital. (William Heinemann Ltd., price 13*s*. 6*d*.)

Synthetic Drugs, by H. Ronald Fleck, M.SC., F.R.I.C., is described as 'a handbook for chemists, physicians and pharmacists'. It is an admirable attempt to summarize the essential chemical, pharmacological and clinical data concerning the more important synthetic drugs now in common use. As a quick-reference book it will prove of value to all three groups for whom it has been written. (Cleaver-Hume Press Ltd., price 70*s*.)

Superannuation for the General Medical Practitioner, by Hugh Barry.—In a booklet of 20 pages Mr. Barry expounds the provision for general-practice superannuation with such clarity that widows' pensions, retiring allowances and death gratuities need no longer hold

any mystery. The fifteen examples given at the end of the booklet cover most of the combinations of circumstances likely to be met. (William Heinemann Medical Books Ltd., price 2*s.* 6*d.*)

Rehabilitating the Tuberculous, by Muriel Owen-Davies, A.M.I.A., S.R.N., S.C.M., as its name implies, describes the sources of assistance available for the tuberculous patient in his restoration to health and working capacity. It stresses that the main needs at present are greater coordination of the available resources and also machinery for making these known to the patient. This is a highly specialized subject, of interest mainly to physicians and social workers at chest clinics throughout the country, where it will be invaluable. (National Association for the Prevention of Tuberculosis, price 5*s.*)

OFFICIAL NOTICE

The Care of Infants in Maternity Units.—This memorandum (H.M. (35)116) draws the attention of regional hospital boards and hospital management committees to the desirability of reviewing the present practice in the care of infants in maternity units. It is pointed out that 'the congregation of a large number of infants in a nursery is not without danger, principally from the spread of infection and less commonly, from accidents'. For instance, in 1952, nine deaths during the first fourteen days of life occurred in hospitals from suffocation or inhalation of regurgitated food, and 16 in 1953. The advantages of keeping babies with their mothers are that the mother-child relationship is firmly established, the risk of infection is reduced, and the infants are not subjected to frequent changes of environment and temperature. Further, 'as the infant is constantly under the eye of the mother and nursing staff any abnormal sign is likely to attract attention at once and the necessary action be taken without delay'.

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended December 31, 1954. *Part II. On the State of the Public Health* is the annual report of the Chief Medical Officer. The infant mortality rate reached a new low record of 25.4 per thousand related live births. This steady fall in the infant mortality rate is bringing into increasing prominence the problem of prematurity. Nearly 7% of notified live births were premature, and of 45,118 premature babies born in 1954 there were 3,773 who did not live more than twenty-four hours. Further, of the 16,000 stillbirths which occur annually nearly half are premature.

The position with regard to the infectious diseases is satisfactory on the whole. During the year no case of smallpox was notified, there was a further reduction in the notifications of diphtheria (167), and the mortality for scarlet fever remains low. On the other hand, there was a further large increase in the incidence of dysentery: at 31,858 the incidence was one and a half times that of 1953. Fortunately, the mortality is low: the ratio of deaths to notifications was only 0.1%. In the last six years mortality from tuberculosis has fallen by 64%, but the notifications of respiratory tuberculosis have fallen by only 14%. The incidence of food poisoning is still rising: the number of incidents was 14% higher than in 1953. Again, the principal source of infection was the made-up meat dish.

In the report on the National Blood Transfusion Service it is noted that in 1954 the regional transfusion centres issued more blood than in any previous year, and the total was slightly more than three times that in 1946. Altogether, hospitals received 620,000 donations of blood collected by the Service. On this the report comments: 'one wonders whether the steady increase in the use of blood from year to year is entirely justified since the number of hospital beds is not increasing and the average stay of the patient in hospital is not diminishing at rates which would explain more than a small part of the increase'. Greater use of dried plasma would ease the situation considerably. (H.M. Stationery Office, price 8*s.* 6*d.*)

Report of the Committee on Maladjusted Children is the first systematic review to have been made of the various services available. It deals with prevention as well as treatment. Its many recommendations include the establishment of a comprehensive child guidance service in the area of every local education authority, and that more use should be made of day treatment. Residential treatment should be given only if there is no hope of treating the child successfully at home. On the question of independent schools, it is recommended that local education authorities should be permitted to maintain maladjusted pupils only in those independent schools which are recognized by the Ministry of Education. (H.M. Stationery Office, price 6*s.*)

THE PRACTITIONER: 50 Years Ago. See pages 117-118

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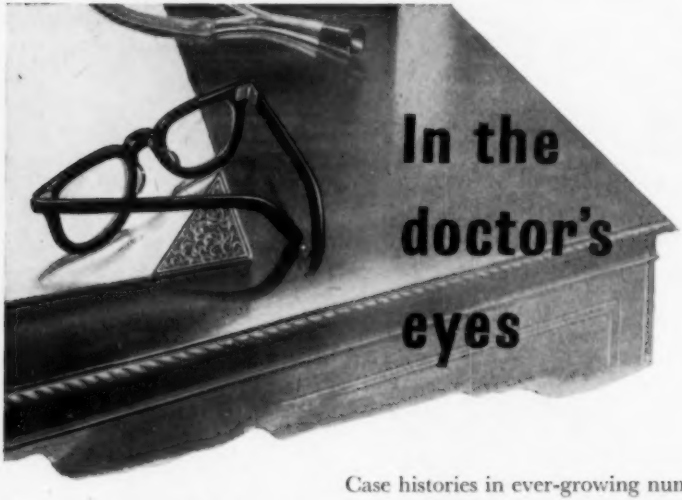

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THE PRACTITIONER
Fifty Years Ago

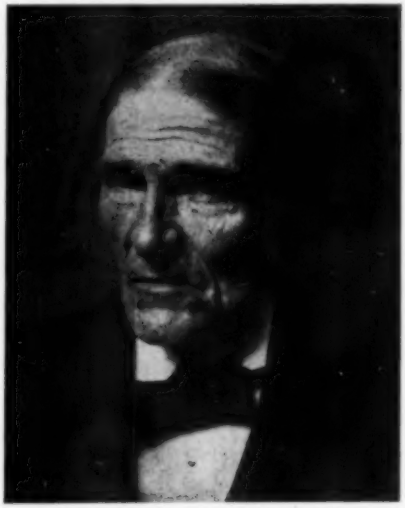
'O, call back yesterday, bid time return'.—*Richard II*, Act iii, sc. 2, l. 69.

JANUARY 1906

IN greeting his readers at the opening of a New Year, the Editor expresses his thanks to the medical profession for the large measure of support which he continues to receive from them: 'This has placed *The Practitioner* in the front rank of British medical journals in point of bona fide circulation, and as the number of subscribers shows a steady increase, we feel justified in concluding that the journal satisfactorily meets the needs of the average practitioner. Another evidence of growth is the number of original contributions offered for publication, and these, while making the work of selection somewhat embarrassing, ensure the maintenance of a high standard of quality, scientific and literary. A feature . . . which seems to find particular favour with readers, and which has elicited many expressions of approval in several of our American contemporaries, is the allotment of whole numbers to the exposition and discussion from every point of view of important subjects of practical interest'.

The most wonderful feature in the career of Sir John Scott Burdon-Sanderson, Bt, Regius Professor of Medicine at Oxford, who died on November 23, 1905, according to 'Notes by the Way', was 'the amount of really good work he managed to do. We are told by the wise that nothing of any value is ever achieved except by concentration. Yet Sanderson's mind always seemed to be elsewhere. It has been said by some of his necrologists that the stories of his absence of mind are myths. This statement, like Mr. Pickwick's views on politics, according to Count Smorltork, "surprise by himself". His absence of mind was open and palpable to feeling as to sight. When he was physician at the Brompton Hospital he used to leave his hat on one bed, his overcoat on another, his umbrella on a third, and his stethoscope anywhere. The objects thus scattered about in his progress through the wards had to be collected by the nurses and clinical assistants who attended him. . . . The story of his boiling his watch while holding an egg in his hand is in La Bruyere's *Caractères*; but there seems to be some foundation for the suspicion that in his laboratory he once lunched on a frog and was afterwards found deeply contemplating a sandwich'.

Writing on the combination of 'the scattered medical societies of London into one strong body', the Editor raises a protest against the proposed title 'Royal Society of Medicine': 'It might be described in legal terms as a colourable imitation of the title of the Royal Society, and as such its use might fairly be objected to by that body. Even if the Royal Society did not formally oppose, it is well known that there is a faction among its fellows who would be glad to use the title as a pretext for excluding doctors. To a medical candidate they would say plausibly enough: "You have a Royal Society of your own, that is the place for you" '.



Sir John Burdon-Sanderson, Bt, 1828-1905

Fifty years ago typhoid fever was a common disease in English hospitals, and its description occupied the position of honour in Osler's 'The Principles and Practice of Medicine'. Many of Osler's papers dealt with the history, epidemiology, and clinical aspects of typhoid, and he was fond of saying that if a student knew this disease thoroughly, he knew half medicine because of its many complications. The first of the 'Original Communications' in the January

1906 number is from his pen and is entitled 'Œonvulsions in Typhoid Fever': 'In our experience among between 1,500 and 1,600 cases at the Johns Hopkins Hospital, convulsions have occurred in 8. I have looked over the histories and have grouped them according to the conditions under which the convulsions happened. . . . The prognosis is not very grave, considering the alarming nature of the complication. Of the eight cases, only three died, one of them from perforation, and one of intercurrent tuberculous meningitis; only one died directly from the cerebral condition causing the convulsion'.

'Is the generally accepted treatment of uric acid satisfactory?' asks James F. Goodhart, M.D., LL.D., F.R.C.P., Consulting Physician, Guy's Hospital. 'If the man who passes uric acid can only substitute a diet that is free from materials that produce it, it can no longer be formed within him . . . he will be freed from his leprosy, and henceforward, if he abides by the prescribed regime, all will go well with him. Is this so? . . . Clinical observation teaches us that in many cases you may . . . absolutely exclude all uric acid forming food of whatever kind you assume that food to be, you may wither up your patient into a shrivelled, juiceless, prematurely aged being, and there will yet, by some means or another, under favouring conditions, be squeezed out of his tissues enough uric acid to form a large deposit of red crystalline matter in his urine. There is still a very large *x* outside diet still to be grappled with and explained by physiological chemistry'.

Sir Lauder Brunton, M.D., F.R.S., Consulting Physician, St. Bartholomew's Hospital, discusses the 'Physiological Action of Tea as a Beverage'; Robert Hutchison, M.D., F.R.C.P., Assistant Physician to the London Hospital, deals with 'The Present Position of Dietetics'; Hugh M. Rigby, M.S., F.R.C.S., Surgeon in Ordinary to the Prince of Wales, reviews 'Some Recent Work on the Surgery of the Stomach and Appendix'; and A. Rendle Short, M.D., late House Physician and Casualty Officer, Bristol General Hospital, writes on 'Œdema of the Face'.

The 'hero' of the series 'Famous Hospitals and Medical Schools' this month is Guy's Hospital. In 'By-Paths of Medicine. Some Medical Worthies of Bath' we read that Tobias Smollett in his 'Essay on the External Use of Water' (1752) 'set himself to prove that for hydrotherapeutic purposes the mineral waters of Bath had little advantage over any other water. It is not surprising that he left Bath soon afterwards'.

'Novelties and Notices' mention that 'Messrs. Cadbury Bros. have again forwarded samples of their much appreciated specialities'.

W. R. B.

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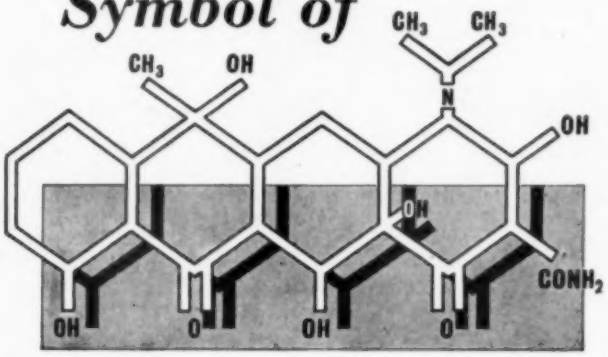

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MOTORING NOTES

The Standard Vanguard

By ROBERT NEIL

ONE of the few new cars shown at the Motor Show in October, the Standard Vanguard drew considerable attention because of its greatly improved appearance. The most important technical change from the preceding model is that the wheelbase has been lengthened, from 7 ft. 10 in. to 8 ft. 6 in., which has allowed the body to be built lower, and the rear seat to be placed well in front of the rear axle.

THE ENGINE

The engine remains basically unchanged from the one first introduced with the Vanguard in 1947, but some interesting modifications have been made, which have had the effect of increasing the performance and improving the fuel consumption. The inlet ports of the engine have been modified to allow better breathing, and the additional power obtained has allowed the gear ratios to be raised, with the result that engine speed—and so the fuel consumption—have been reduced. During the years since its introduction the Vanguard engine has earned a high reputation for long life, and this is almost certainly due to the use of wet cylinder liners, which are made of a specially wear-resistant material; owing to their thorough contact with the coolant these prevent distortion from local hot spots.

THE BODYWORK

The more forward mounting of the rear seat allows the entire passenger load to be poised between front and rear wheels, which prevents pitching on uneven surfaces. This also allows the rear doors to be in front of the rear wheel arches, so that entry and exit are made easier. No separate chassis is used on the car. Instead the body and framework form one integral construction but, as this method of construction tends to pass road noises in to the car interior, the front suspension is carried on a separate assembly, which is attached to the car at four points with rubber insulation. The suspension itself is by coil springs at the front, and by semi-elliptic leaf springs at the rear, and assistance and control are by telescopic hydraulic dampers.

The car is well fitted, particularly bearing in mind its reasonable price. Both front and rear seats are provided with folding central armrests, and all four doors have combined armrests and door pulls. Also included in the standard equipment are an efficient car heater and demister, and a windscreen washer. The lines of this new model are admirable, and the use of a cross-flow radiator makes the use of a horizontal air entry logical. The instruments are of sensible type, with clear white figures on black faces—the best type of dial—and they are indirectly illuminated by a pleasing green light. The fuel tank is placed immediately behind the rear seat squab. This allows for a large luggage boot. As the spare wheel is carried in a separate compartment, the boot has a completely flat floor.

The driving compartment of the Standard Vanguard. The small switch fitted on the arm protruding from the steering column housing operates the overdrive; the gear lever is hidden behind the wheel. The sensible grouping of the instruments in front of the driver can be noticed, and also the adequate room between the pedal controls

THE OVERDRIVE SYSTEM

The Laycock-de Normanville overdrive system has long been supplied with the Standard Vanguard, and in its latest form—operative on both second and top gear—it is available as an optional extra. The use of this overdrive in effect converts a simple three-speed gearbox into a five-speed gearbox, with the advantage that the overdrive gears are obtained by a flick of a finger on a small switch fitted beneath the steering wheel. The greatest advantage of the overdrive is that having reached one's selected cruising speed on top gear—whether it be 50 or 75 m.p.h.—it is only necessary to flick the overdrive switch, and the same road speed is maintained, but with a great reduction in engine speed. As an example, an engine speed of 3000

r.p.m. equals a road speed of 54 m.p.h. on top gear, but on overdrive the speed is 69 m.p.h. It can easily be appreciated that for a given road speed greater silence and smoothness can be enjoyed when using the overdrive. In addition it assists in reducing the fuel consumption, especially at high cruising speeds.

SOME COMMENTS

After some experience with the car it is possible to use the steering-column-mounted gear lever, and the overdrive switch, simultaneously, so that one can accelerate the car through all five gears: first, normal second, overdrive second, top and then overdrive top. The car can be regarded as an 80 m.p.h. one, but it is interesting to note that, despite this good speed, it has been possible to obtain a fuel consumption in the region of 30 m.p.g. The average throughout my test was 29.5 m.p.g., and I should point out that this was obtained under conditions of very hard driving, including the performance tests.

Owing to the very good forward vision granted by the low bonnet line the car feels smaller and neater than it actually is. The driver's vision is spoilt to some extent by the rather thick windscreen pillars which obscure the view, particularly on sharp right-hand corners. The model I tested gave the impression of being a much better car on the open road than in town traffic. In the latter conditions the steering was definitely on the heavy side. It may have been a fault on the individual car I tested, but the suspension and the upholstery seemed too firm; this is a fault which might correct itself after a greater mileage.

The new Standard Vanguard saloon

One feature of the car which I do not like is the excessive size of the combined rear and stop lights. More than once when driving in thick traffic it only required a glance in the mirror to realize that following motorists were nearly blinded by the excess of light. Drivers of over-average height might find that the seat adjustment provided is not sufficient to prevent the steering wheel impeding their right leg, when moving from the accelerator to the brake pedal.

In general this latest model from the Standard factory offers logical development from its predecessors; appearance, comfort, performance and economy all show improvements.

STANDARD VANGUARD DATA

Basic Price: £599	Wheelbase: 8 ft. 6 in.
Purchase tax: £300 17s.	Track: 4 ft. 2½ in. (front)
Capacity: 2,088 c.c.	Track: 4 ft. 3 in. (rear)
Cylinders: Four	Length: 14 ft. 3½ in.
Valves: Overhead	Height: 5 ft. 1 in.
Oil filter: By-pass	Width: 5 ft. 7½ in.
1st gear: 15.22 to 1	Weight: 24½ cwt.
2nd gear: 7.18 to 1	Ground clearance: 7¼ in.
3rd gear: 4.3 to 1	Fuel capacity: 12½ gall.
Overdrive 2nd: 5.6 to 1	Oil capacity: 11½ pints
Overdrive top: 3.35 to 1	Water capacity: 14½ pints
Brakes: Lockheed hydraulic	Fuel consumption: 29.5 m.p.g.
Max. speed: 79.4 m.p.h.	Acceleration: 0-60 (all gears) 21.5 sec.
Brakes: 98% efficiency	

WINDSCREEN WASHERS

Most wise motorists, particularly those who use their cars constantly during the winter, use some form of windscreen washer, to avoid the inconvenience of stopping at frequent intervals to clean the screen. A new, and much improved, type is now available, which incorporates a small electric motor to pump the water on to the windscreen. This completely obviates the time lag with the usual type of washer and, as it is entirely independent of the engine, it can be used even when passing another car with the throttle wide open. The type of washer operated by the depression in the induction manifold can fail to do its job when required if the engine is turning over at high speed. Apart from using the washer to clean the screen at intervals on a long run, I find that one often has to use it exactly when passing a heavy lorry with inefficient rear mudguards. The current consumption of this new washer is very low, and one reservoir-full is estimated to wash the screen thirty times.

Robert Neil will be pleased to deal with any motoring queries our readers care to submit to him. These should be addressed to him c/o 'The Practitioner,' 5 Bentinck Street, London, W.1.

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THE new method of manufacture will shortly be put into full-scale production so that, from start to finish, Cortelan (cortisone Glaxo) will be made in the United Kingdom from materials produced in sterling areas.

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PRODUCT	POTENCY	FORM OF HORMONE	PACK
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	25 mg.	cortisone acetate	Bottle of 40 Bottle of 500*
EF-CORTELAN STERILE SOLUTION (for preparing intravenous infusion)	100 mg./20 cc.	hydrocortisone free alcohol	20 cc. ampoule
EF-CORTELAN TABLETS	20 mg.	hydrocortisone free alcohol	Bottle of 100

LOCAL

PRODUCT	POTENCY	FORM OF HORMONE	PACK
EF-CORTELAN INTRA-ARTICULAR INJECTION	25 mg./cc.	hydrocortisone acetate	6 x 1 cc. ampoules 5 cc. vial
EF-CORTELAN SKIN LOTION	½% 1%	hydrocortisone free alcohol	20 cc. 'squeeze' bottle
EF-CORTELAN SKIN OINTMENT No. 1 (non-greasy base)	1% 2½%	hydrocortisone acetate	5 gm. tube 15 gm. tube 50 gm. jar
EF-CORTELAN SKIN OINTMENT No. 2 (greasy base)	1% 2½%	hydrocortisone acetate	5 gm. tube 15 gm. tube 50 gm. jar

OPHTHALMIC

PRODUCT	POTENCY	FORM OF HORMONE	PACK
CORTELAN EYE DROPS	1%	cortisone acetate	3 cc. dropper bottle
CORTELAN EYE OINTMENT	1%	cortisone acetate	3 gm. tube
EF-CORTELAN EYE DROPS	1%	hydrocortisone acetate	3 cc. dropper bottle
EF-CORTELAN EYE OINTMENT	2½%	hydrocortisone acetate	3 gm. tube

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Active principles: Pentaerythritol tetranitrate 10 mg.

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How severe a gastric irritant is aspirin?

FURTHER RESEARCH has now been done into the irritant effects of aspirin upon the gastric mucosa. A detailed report on this work appears under the heading "Aspirin and Ulcer" in the B.M.J., July 2, 1955.

The summary of the discussion appended to this report is as follows:

"Aspirin is a serious gastric irritant, particularly in peptic ulcer patients."

Here is a further extract from the report:—

"In conclusion it is suggested that aspirin should never be given to patients with peptic ulceration, or indeed to those who have any gastric intolerance to it, however mild. Such an instruction should be given a prominent place in peptic ulcer advice charts, usually in place of much that could be safely left out. Some of these patients took aspirin on a full stomach only in powder form, with serious results, and, although this method almost certainly mitigates its irritant effects, it does not guarantee immunity. Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly the incidence of haematemesis and exacerbations of ulcer symptoms."

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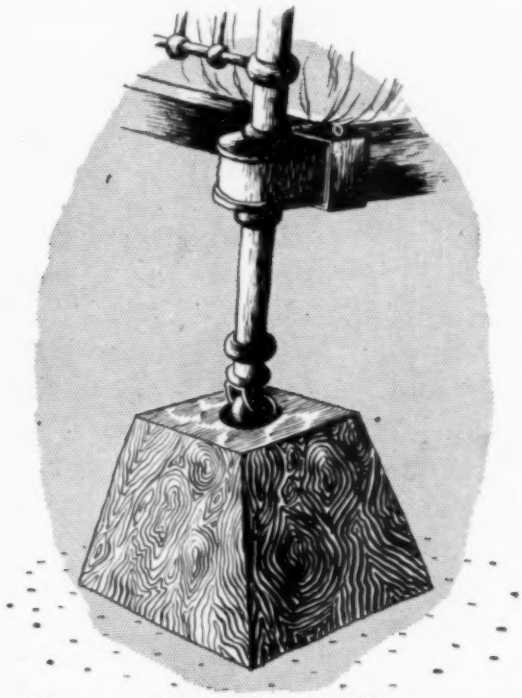

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injection maintains it for one to two hours. MEPHINE is indicated in circulatory collapse complicating accident or illness ; post-operative hypotension ; spinal anaesthesia ; cardiac surgery ; myocardial infarction. MEPHINE has *no cardiac or cerebral side effects.*

PACKING :
1 c.c. Single-dose Vial containing 15 mg. Mephine base. 10 c.c. Multi-dose Vial containing 15 mg. Mephine base per c.c.

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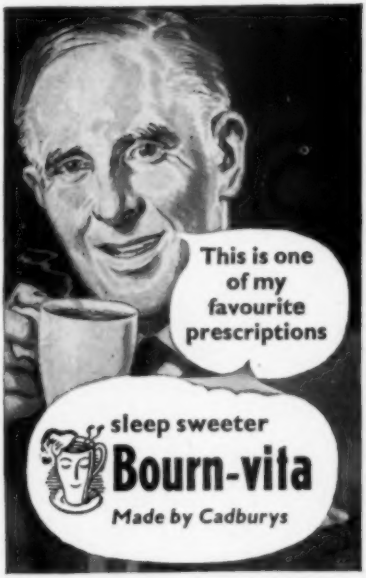

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[1] *Practitioner* (1954). Vol. 172, p. 183.

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